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Some issues of nanometals applications in cancer treatment

Abstract: Nanotechnology and the use of innovative materials, such as nanoparticles, have created a new and effective approach to fight cancer. Several achievements in cancer therapy using metal nanoparticles and challenges facing them are presented in the current review. Cancer therapy requires teamwork with a multidisciplinary approach. It has different levels according to the type of cancer, including chemotherapy (induction, neoadjuvant, adjuvant, consolidation or maintenance chemotherapy), radiotherapy and surgical resection. Nanometals and nanodrugs may be used on the different levels of cancer therapy, especially in chemotherapy. Platinum (Pt)-based drugs are one group of the most effective drugs used for cancer chemotherapy. Gold nanoparticles are the other group of nanometals commonly used in cancer treatment. Although effectiveness of nanometals including gold-, silver-, and iron-based, has been investigated on different cancer cell lines and animal models both in vitro and in vivo, their effectiveness should also be explored from the viewpoints of evidence-based medicine.

Key words: cancer, chemotherapy, nanoparticle, nanometal, platinum, gold, silver.

Introduction

Cancer therapy is a multidisciplinary effort that requires involvement of different specialties, each providing specific services to the patient with the aim of ensuring that the patient receives optimum care and support. However, any innovation cannot be used directly in clinical practice, since any novel idea may intervene in the accepted procedure of therapy. Such challenges are now going to be solved thanks to evidence-based medicine (EBM) [1; 2]. Use of innovative materials, such as up-conversion nanoparticles, nanogold, quantum dots, magnetic nanoparticles and nanodiamonds has created a new and effective approach to fight cancer. Use of nanoparticles led to many opportunities in cancer diagnosis and treatment. Hybrid proteins and nanostructures can be used to affect in different ways affecting the tumor, for instance, by creating magnetic field, temperature, light, etc. To date, substantial accomplishments have been achieved, but in spite of all successes, many problems like biocompatibility, selective drug transfer, pharmacokinetics, safety and success of the chosen treatment remain unresolved [3].

In this regard, we performed this review to discuss novel achievements of metal nanoparticles in cancer therapy and challenges facing them.

Multi-subject cancer therapy

Cancers are usually represented by hematologic malignancies and malignant solid tumors [4]. Solid tumors are mainly carcinoma (epithelial origin) and sarcoma (mesenchymal origin), transition from epithelial origin to mesenchymal origin may occur as well [5; 6].

The general protocol of cancer therapy includes different levels of chemotherapy, radiotherapy, medical and palliative therapy, and surgery. In hematologic malignancies, the first level is induction [7]. The chemotherapy at this level results in reduction of malignant cell numbers from $10^{11}$ to $10^9$ (approximately 99%) within one month. The clinical manifestation of this reduction is named complete remis-
sion [8]. Patients are then prepared for consolidation therapy (a 1 to 2-month period). Thereafter, the remaining malignant cells should be destroyed during a 1 to 2-year period of maintenance therapy [9]. In solid tumors, surgical resection is essential. Steps preceding and following may be or not to be performed according to the type of cancer, its stage and clinical judgement of practitioners. Neoadjuvant chemotherapy precedes the surgical resection. It results in clearance of tumor margins and helps surgeons to differentiate tumor margins during resection. Although level wise neoadjuvant chemotherapy of solid tumors is equivalent to induction level in treatment of hematologic malignancies, reduction of malignant cell numbers from $10^{11}$ to $10^9$ in solid tumors occurs after surgical level [10]. Level after surgical resection is called adjuvant chemoradiotherapy. The resection procedure can be R0 (without microscopic residue), R1 (without macroscopic residue) or R2 (with macroscopic residue). R2 is also called as palliative resection. Palliative therapy is used for the patients who are at end stages, have older ages or poor prognosis. Such patients are referred to palliative medicine ward [11]. We have indicated a comparison of cancer therapy levels in hematologic and solid malignancies through the lens of number of malignant cells in Figure 1 and Table 1.

Figure 1 – Comparison of cancer therapy levels in hematologic and solid malignancies assessed by the number of malignant cells

Figure 1 shows that different levels are required to reduce the number of cancer cells in patient. All the levels should be completed to reduce the probability of recurrence. Nanodrugs can be used at these levels. For solid tumors, surgical resection is always necessary, except metastatic cancers.

Table 1 – Levels and principles of cancer therapy in general

| Type of malignancy (cancer) | Hematologic | Solid tumor |
|-----------------------------|-------------|-------------|
| **Level of therapy** | Method | Outcome | Level of therapy | Method | Outcome |
| Induction | Chemotherapy | Complete remission | Neoadjuvant | Chemotherapy | Visibility of margins |
| Consolidation | Chemotherapy/BMT | Clearance of malignant cells | Resection | Surgery | Clearance of malignant cells |
| Maintenance | Chemotherapy/Radiotherapy | Prevention of relapse | Adjuvant | Radiotherapy/Chemotherapy | Prevention of relapse |
| Palliative (if failure to cure) | Clinical and medical care | Increased quality of life | Palliative (if failure to cure) | Clinical and medical care | Increased quality of life |

Note: BMT: bone marrow transplantation

Table 1 shows the levels of cancer therapy in detail. Complete remission belongs the signs and symptoms which patients have them at the time of diagnosis. In solid tumors, neoadjuvant chemotherapy helps to increase visibility of the tumor margins for better surgical resection; in addition, a partial remission may be observed.

Molecular bases of cancer and mTOR signaling pathway

In general, if cell replication signals uncontrollably overcome cell cycle suppression signals a neoplastic tissue will be formed. Genes activating cell cycle are called proto-oncogenes and genes inhibit-
ing cell cycle are called tumor-suppressor genes. The examples of proto-oncogenes are human epidermal growth factor receptor 2 (Her2), KRAS, beta-catenin, cyclin D1, c-Kit, vascular endothelial growth factor (VEGF) and other. Monoclonal antibodies are used to target the products of these genes. For instance, trastuzumab targets Her2, imatinib targets c-Kit and bevacizumab targets VEGF [12].

Mammalian target of rapamycin (mTOR) is a center for multiple cell growth pathways and can be connected with multiple other proteins, which play important roles in cell growth. This system consists of two complexes; one of them is mTOR complex 1 and the other one is mTOR complex 2, which manage cellular processes by phosphorylation of major translation regulators, such as ribosomal S6 kinase and eukaryote initiation factor 4E binding protein. mTOR is sensitive to physiological responses dependent on cellular levels of oxygen, nutrients and energy. Due to its important roles in various cellular processes and diseases, mTOR is considered the molecular aim. mTOR is involved in obesity, depression and cancer and the importance of these diseases lead to production of the rapamycin, which in turn can inhibit mTOR and its analogs. mTOR signaling can be disrupted by genetic mutations, such as mutation in phosphatase and tensin homolog (PTEN) gene and cause several cancers like prostate, melanoma, breast, lung, endometrial, brain, thyroid, bladder and renal cancers. mTOR activity in both normal and cancer cells has been inhibited using different types of nanoparticles and results in reduction in the level of phosphorylated mTOR and subsequently mTORC1 catalytic activity [13-16].

Use of metals and metal nanoparticles in diagnosis and treatment of cancer

Nanometals (metal nanoparticles) can be used both in diagnosis and treatment of cancer, including targeted drug delivery [17], tracking of malignant cells [18], magnetic-based hyperthermia treatment [18], etc. The latter results in expression of heat shock proteins by tumor cells and induction of apoptosis [19]. We summarized specific nanoparticles used for the specific cancer cell lines in Table 2 [20-37].

| Nanoparticle (type) | Cancer (cell line) | Summary of findings | Ref. |
|---------------------|--------------------|---------------------|------|
| Gold (PEGylated)    | Reticulo-endothelial system | The aim of this study was to produce gold nanoparticles using plant-mediated phytochemical extracts and take the conjugate particularly to the tumor. It was proved that PEGylated gold nanoparticles can be used as delivery vehicle for targeting small biomolecules (antibody etc.) to the tumor location. | [23] |
| Gold (Au@QCS-GA-FA) | Lung cancer cells (CHAGO) | Quaternized chitosan-gallic acid-folic acid stabilized gold nanoparticles (Au@QCS-GA-FA) has enough potential to use as an anti-cancer agent. | [29] |
| Gold (Dox*FA-GO@Au) | Ehrlich Ascites Tumor cells; EAT cells (breast cancer); MCF-7 cell line | This study showed that gold nanoparticles can play important role in tumor management. | [21] |
| Gold (lycopene-nanogold nanoemulsion) | Colon cancer cell line (HT-29) | The aim of this study was to produce a nanoemulsion by the use of gold nanoparticles and lycopene and study the effect of this nanoemulsion on HT-29 colon cancer cell line. According to this study LP-nanogold nanoemulsion have sufficient effect the treatment of colon cancer. | [27] |
| Gold (Hyaluronic acid-fabricated nanogold) | Lung cancer cell line (A549) | Inhibitor of apoptosis protein-2 (IAP-2) was driven into A549 cells by the use of gold nanoparticle and hyaluronic acid (AuNP-HA) and results to a reduction in the cell proliferation. | [31] |
| Silver (Biogenic silver nanoparticles) | Human breast cancer (MCF-7 cell lines) | Biogenic silver nanoparticles showed their impressive role in inhibiting of MCF-7 cell lines. | [30] |
| Silver (Plant derived silver-nanoparticle) | Colorectal cancer cell line (HCT116) | PD-AgNP leads to apoptosis in colon cancer cells. | [34] |
| Nanoparticle paclitaxel (NP PTX) | Lung Cancer | Nanoparticle paclitaxel (NP PTX) caused G2/M phase cell cycle pause and changed the microtubule dynamics resulting in cell death. | [25] |
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| Nanoparticle (type) | Cancer (cell line) | Summary of findings | Ref. |
|---------------------|--------------------|---------------------|------|
| Silver              | Human breast cancer cells (MCF-7) | AgNPs signified sufficient cytotoxicity impact against MCF-7 at minimal dosage. | [35] |
| Nanodiamond/nanoplatinum | Breast cancer cells (4T1) | Nanodiamond/nanoplatinum can be used as cancer therapy agent owing to its ability to reduce cell stiffness. | [24] |
| Silver              | Prostate cancer cells (PC3) | Prostate cancer cells can be destroyed by cytotoxic effects of Nanosilver. | [22] |
| Silver (TAT-modified nanosilver) | Multidrug-resistant (MDR) cancer-melanoma | AgNP-TAT is a strong anticancer nanoparticle and can inhibit MDR, non-resistance cells and the tumor growth. | [32] |
| Silver              | Human oral squamous cell carcinoma (HSC-3) | The main purpose was the comparison of intracellular impacts between silver nanoparticles (AgNPs) conjugated with nuclear and cytoplasmic targeting peptides and peptide-conjugated gold nanoparticles (AuNPs). Treated cell with AgNPs showed DNA damage and apoptosis. | [20] |
| Epigallocatechin-3-gallate-gold nanoparticles (EGCG-pNG) | Bladder cancer | EGCG-pNG as a antitumor agent can inhibit tumor cell growing owing to apoptosis. | [26] |
| Fluorophore-nanoparticle | Breast cancer | Fluorophore-nanoparticle can be utilized as a designed complex to target breast cancer by emitting fluorescence conditionally. | [36] |
| Gold                | Liver cancer       | Nanogold revealed its potential for inhibiting of the angiogenesis and growth of liver cancer cells because of inhibition of the VEGF165-induced signaling. | [33] |
| Gold                | Breast cancer      | The aim was to develop a tumor-specific multi-functional, nano-entity which is able to detect and treat cancer. Gold-coated Fe3O4 nanoparticles are tumor-specific nano-agents and can play important roles in detection and hyperthermia for breast cancer. | [28] |
| Gold                | Colorectal carcinoma cell line (HT29) | The goal was to study that AuNPs can influence the epithelial origin cell lines: continuous and oncogenic. Cell line of HT29 showed sensitiveness to the effects of AuNPs. | [37] |

Based on results, platinum (Pt)-based drugs are some of the most effective drugs used for cancer chemotherapy. One of the efficient Pt-based anti-tumor drugs is Cisplatin (Cis-diamminedichloroplatinum-II). It was approved in 1978 and is used for treatment of various cancers such as testicular, prostate, bladder and lung cancers. Therapeutic function of Pt-based drugs is binding to DNA and stopping its replication. Cisplatin cannot be used for all types of cancers and resistance to it has been observed. Pt-based complexes showed promising cytotoxic effect due to their structural properties [38; 39]. Other than conventional use of this metal, Pt-based nanoparticles have been studied. These particles have radiosensitizing properties in comparison to metal atoms of Pt [40].

Gold (Au) nanoparticles are commonly used in cancer treatment and diagnostics. For instance, combinations of gold nanoparticles with anti-tumor marker antibodies have been used as biosensors [41]. Due to their physiochemical properties, gold nanoparticles can be used for hyperthermia-based treatment of cancer [42]. Their possibility to act as radiosensitizers has also been shown [40].

Silver (Ag) is known as a metal with antimicrobial and anticancer effects. Previously, silver containing compounds have been shown to have antimicrobial and anticancer effects via induction of necrosis and late apoptosis [43]. According to these effects, nanoparticles of silver are also used [44]. Silver nanoparticles are usually synthesized by medicinal plants (green nanoparticles) [45].

Iron is another metal used in cancer therapy. It is suitable for heat induction. It has been previously proved that magnetic nanoparticles can destroy tumor cells by heat delivery and use of alternating electromagnetic field. Magnetic materials, such as iron oxide (Fe₃O₄ or Fe₂O₃) are the most used materials.
for hyperthermia. Nanoparticles can be employed as tumor hyperthermic treatment because of their ability to be utilized as a heat guide, where their sufficiency depends on their size. The best size of the particles to get heated well is within the range of 10-30 nm. Non-invasive hyperthermic therapy may be feasible by heating a tumor model containing nanoparticles. Absorption of near-infrared reflectance can be improved using gold nanoparticles. Utilization of coated Fe$_3$O$_4$ nanoparticles with gold is a useful method for optical/thermal markers for seamless diagnosis and therapy in a minimally invasive way. This approach has been used towards the breast cancer cell lines [46; 47].

Medical plants and antioxidants can be used for their anticancer effects as well as their pain relieving effects [48]. For pathophysiology of cancers, role of mutilation in apoptotic related genes [49] and angiogenic factors was investigated [50]. We also found that immune cells, such as natural killers might be involved in cancer [51].

**Conclusion**

This review was aimed to investigate the use of nanometals gold-based, silver-based, platinum-based and iron-based in cancer treatment. According to literature, specific metal nanoparticles can inhibit cell lines of different cancers based on *in vitro* experimental studies. *In vivo* studies were focused on magnetic, heat induction and ability to track effects. Metals (as single atom or in combination with other compounds) had been previously used in different diseases. Cancer had been a major concern and hence metals were studied for cancer treatment. Nanotechnology was added to this idea and therefore metal nanoparticles were innovated. They are used according to their targeted effect, magnetic potencies and heat induction as well as tracking cancer cells for diagnostic aims. Use of nanoparticles should not intervene with the accepted levels of cancer therapy. Therefore, such agents should be used as a combination therapy and levels of evidence should be regarded and updated.

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