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Review Article

Inorganic Compounds Going NANO

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Abstract

Transition-metal complexes have shown significant anti-tumour potential and have advanced towards clinical trials. However, tumour cells often develop resistance to chemotherapeutics, which couple to the inherent compound's' toxicity and solubility hampers their translation to the clinics. Therefore, besides the tremendous efforts to synthesise and characterise novel compounds, it is essential to create new drug delivery systems that circumvent these problems, allowing specific and selective delivery of drugs to tumour cells, thus decreasing the required dose and reducing side effects to the healthy tissue. Nano biotechnoloy has been providing for innovative solutions to address this challenge, via the smart design of nano formulations suitable for targeted delivery to the tumour microenvironment. In this review, we discuss recent nano systems combined with medicinal chemistry in cancer therapeutics, focusing on the clinical translation of such systems.

INTRODUCTION

The discovery of cisplatin by Rosenberg and colleagues in 1965 was a landmark on the use of inorganic metal complexes as chemotherapeutic agents in cancer [1]. One of the major areas of medicinal chemistry is the application of inorganic compounds, or molecules bound to a metal centre, to cancer therapy (for a review see [2-4]). However, inorganic compounds toxicity in tumour adjacent or distant healthy cells is usually high due to the lack of specificity. There is, therefore, a need for new drugs with an improved spectrum of efficacy and lower toxicity. Also, there has been an increasing concern related to the surge of multidrug resistance (MDR) by cancer cells. Resistance to treatment may be acquired or intrinsic, both entailing treatment failure [5]. Despite the translation of platinum based metal complexes to clinical practice and their wide application in treatment of several types of tumours (e.g breast cancer) [6], in the last few years, efforts have been made for improving the efficacy of inorganic compounds and reduce their side effects. Such developments have included the use of nanobiotechnology towards targeted nanovectorization systems, bypassing biological barriers and delivery the drug directly to target cells in therapeutic concentrations, whilst sparing the healthy tissues to the deleterious effect of such chemical compounds [7].

In this review we intend to address the main mechanism of action of platinum- and non-platinum based metal compounds, already FDA approved, in clinical or pre-clinical phases as well as problems that still have to be addressed. The combination of the most promising metal compounds with the rising benefits of nanobiotechnology could be the future of cancer therapy.

INORGANIC METAL COMPOUND IN CANCER THERAPY

Metals and mode of action

Following the success of cisplatin as an antitumor agent, several other complexes containing platinum or other metals such as ruthenium, gold, titanium, copper, iron, rhodium, vanadium, and cobalt have been proposed with less toxicity and selectivity towards tumour cells [8]. A punctual change in metallic centre, oxidation state, ligands, geometry or even in coordination number, lead to different reactivity, affecting the drug's mechanism of action [9], such as disturbance of cellular redox homeostasis [10]. For a more complete review on synthesis directions towards the understanding of various transition metals compounds used in biomedical applications please see [3,4,11-13].

The metal may have a functional or a structural role, acting as an *in vivo* carrier for active ligands or as *in vivo* catalyst or behave as photosensitizer [14]; they coordinate ligands in three dimension configuration, allowing functionalization with groups designed for specific molecular targets. Despite the high number of promising metal complexes candidates in (pre) clinical studies [15-17], only a few number of metal complexes have been translated to clinical phase I and phase II studies so far [9,16].

Platinum compounds

Cisplatin is the most well-known and characterized anti tumour drug, binding to DNA purine bases, forming inter-and intra-strand DNA adducts that ultimately induce apoptosis

[18,19]. More recently, Oxaliplatin, the first FDA-approved drug with similar therapeutic results as cisplatin, has been used as substitute of cisplatin with no expressive acquisition of multidrug resistance due to an immunogenic response dependent of the toll-like receptors [19,20]. Satraplatin, another platinum compound in advanced clinical trial phases, is another potential candidate for cancer therapy that, by being more lipophilic, shows improved pharmacokinetic properties. Another advantage is that satraplatin-induced adducts are not recognized by DNA mismatch repair proteins, which decreases the potential surge in resistance [21,22].

Non-platinum metal compounds, a promising future – Ruthenium, Titanium and Gallium

Despite almost 50% of chemotherapy treatments include platinum compounds [23], other transition metals show antitumour potential and are already in clinical trials.

Ruthenium appears to be the next transition-metal to translate to the clinics due to specific properties, such as:i) the ability to promote exchanges between a O- and N-donor molecules identic to platinum drugs; ii) the octahedral geometry allowing binding to nucleic acids; iii) may exist in different oxidation states (from II to IV) in biological fluids; iv) in the oxidation state III gives rise to a low reactive pro-drug that can be activated selectively in solid tumours due to its reducing environment (low oxygen content), and v) it is transported to tumour cells by transferrin [24]. This last intrinsic characteristic allows the use of cell mechanism of iron transport allowing reduction of its toxicity [25]. In general, ruthenium complexes inhibit DNA replication, and induce mutations *via* activation of reactive oxygen species (ROS) and reduction of RNA synthesis. Similarly to platinum, the biggest interest in ruthenium is the ability to bind to DNA [26]. NAMI-A and KP1019 consist of two ruthenium (III) complexes that already achieved phase I and II clinical trials, respectively [27]. NAMI-A has selective effect on metastases (particularly lung metastasis) of solid metastasizing tumours, with no associated effect on primary tumour growth but has evidenced some toxicity in pre-clinical studies [28].Despite these toxicity effects (increase creatinine levels in kidneys; histological lesions of glomeruli and tubuli; increased spleen volume with lymphocytic depletion; increase of circulating lymphocytes; alterations of mitochondrial membranes) NAMI-A is currently studied for its application as a second line therapy in the metastatic non-small cells lung cancer after Gemcitabine therapy [28,29].

KP1019 revealed direct antitumour activity after entering the cell through binding to transferrin, by inducing apoptosis via the mitochondrial pathway and also generates ROS and dose dependent toxicity proved to be limited or even in existent [28]. KP1019 has already completed phase I clinical trials with promising results although there were some solubility problems, a reason why NKP-1319, a more soluble analogue has recently entered phase I clinical trials [28,30].

Titanium is a metal biologically compatible that can lead to non-toxic anticancer drugs. Actually, it was the second metal to go to clinical trials, using Ti (IV) species that binds covalently to DNA [31]. Budotitane, a titanium inorganic complex, followed platinum in clinical trials, as a result of proved antitumour activity in colon tumour cells. However, the instability of Ti (IV) compounds in solution due to a rapid hydrolysis at physiological conditions resulted in an insoluble TiO_2 and the loss of antitumour properties leading to disappointed results in phase I clinical trials [32]. Recently, a new class of titanium (IV) complexes, titanium salan complexes, proved to have a higher antitumour activity and hydrolytic stability [33].

Gallium, due to the similarity to ruthenium is able to complex with proteins and ligands that bind iron and may be transported using iron bio-distribution pathways [34]. Gallium nitrate is the first-generation of gallium anticancer compounds, capable to induce apoptosis through activation of Bax, releasing cytochrome c from the mitochondria and activating effector caspases. Phase I and II clinical trials have attested their activity in lymphomas. Unfortunately, malignant cells showed some resistance to this drug and a high level of gallium in plasma associated to kidney toxicity, demonstrated severe dose limitations [34,35].

Why going NANO?

The indiscriminate destruction of healthy cells, the toxicity of conventional chemotherapeutic agents, as well as the development of MDR, support the need to find new effective targeted therapies based on the heterogeneity of the tumour cells [36]. Nanomedicine is a promising and thriving field that applies nanotechnology to medicine, and in particular nanoparticles (NPs) have been successfully applied as drug carriers, in hyperthermia or radiotherapy, photodynamic therapy and photo thermal microscopy [37,38]. The use of nano-sized materials has several benefits like high surface/volume ratios, modifiable structures and adaptable sizes [39], which enhance the potential of nanoparticles as drug carriers either via the enhanced permeability and retention effect (EPR effect) due to tumour vasculature and impaired lymphatic system - passive targeting; or actively targeted to cancer cells *via* functional moieties grafted to the surface [37,40]. Twenty years after Doxil®, the first FDA-approved nano-drug, and less than five years from Abraxane(®), the novel nanoparticle albumin-bound [nab] paclitaxel approved for the treatment of metastatic breast cancer by FDA, there is still a long way towards active drug targeting which allows drug release at the tumor site to improve efficacy and reduce the dose dependant toxicity of chemicals (for a review see [36,41-43]). These novel targeted therapies because of their potential for multi-functionality aims at simultaneously block tumour cell transduction pathways and/or specific proteins to foster cancer cell death while deliver common and already prove as effective inorganic metal compounds specifically to cancer cells, minimizing the undesirable side effects leading to a new era of personalized medicine [36,43].

An increasing number and diversity of nano particles have been proposed as vectorisation vehicles, ranging from polymer-based nano particles to dendrimers, lipid-based nano particles, ceramic nanoparticles, metal nano particles and carbon nanotubes [44]. Table 1 illustrates recent examples of nanovectorized drugs according to nano particle category. Current studies on nanovectorized compounds are comprised mostly of FDA-approved compounds or well characterized drugs as a result of the profound knowledge of the compounds in terms of mechanisms of action, pharmacokinetic and pharmacodynamic properties as well as physic-chemical characteristics.

Table 1: Nano vectorised FDA-approved inorganic compounds enclosing increased anticancer properties compared to free compound (2010-2015). Drug denomination, nano carrier and incorporated inorganic compound, applications, mechanism of action and pipeline status. *FDA-approved inorganic compounds with anti tumour properties.

Drug denomination	Inorganic compound	Nanocarrier	Applications	Mechanism of action	Pipeline Status	Refs.
Polymer-based nanoparticles						
Oxaliplatin vectorized in chitosan nanoparticles	Oxaliplatin*	Chitosan NPs	Cytotoxicityin MCF7 cell line	pH dependent release behaviour	Pre-clinical (*In vitro* studies)	[45]
Carboplatin vectorized in polymethylmethacrylateNPs	Carboplatin*	Polymethylmeth-acrylateNPs	Advanced intra-ocular retinoblastoma	Increases intra-ocular drug concentration	Pre-clinical (*In vivo* studies)	[46]
PLA-NPs loaded with KP1019	KP1019	Poly lactic acid	Cytotoxicity in SW480 and Hep3B cell lines	Stabilizes free compound in water and increases cytotoxicity	Pre-clinical (*In vitro* studies)	[47]
DOTAP loaded with AziRu	AziRu	Cationic lipid DOTAP	Cytotoxic effect in MCF7 and WiDr cell lines	Improved cytotoxicitycomparedto free AziRu	Pre-clinical (*In vitro* studies)	[48]
Lipid-based nanoparticles						
Lipoplatin	Cisplatin*	Liposome	Pancreatic/ Head and Neck/ breast cancer	Combined with paclitaxel for chemotherapy in non-small cell lung cancer (NSCLC)	In clinical trials phase III	[49]
Nanobins	Arsenic trioxide*	Liposome	Female lymphomas	Cytotoxicity in cancer cells and protective effect toovarian cells	Pre-clinical (*In vivo* studies)	[50]
Cationic Liposomal ToThyCholRu	Ruthenium complex (ToThyCholRu)	Liposome	Cytotoxicity in MCF7 and WiDrcell lines	Increased toxicity comparedfree ruthenium complex	Pre-clinical (*In vitro* studies)	[51]
Carbon nanotubes						
Cisplatin encapsulated in multi-walled carbon nanotube capped with functionalized gold NPs	Cisplatin*	Carbon nanotubes	Cytotoxicity in MCF7 cell line	Carbon nanotubes bottles. Increased cytotoxicity compared tofree cisplatin	Pre-clinical (*In vitro* studies)	[52]

Conclusions and future perspectives

Inorganic medicinal chemistry allied to nanotechnology has been providing a major help in cancer treatment. The right nano formulation can bypass biological barriers and deliver the drug directly to the cancer cell, allowing the decrease of drug dosage and avert the healthy cell from the dangerous side effects of chemotherapy [53]. Nanodelivery systems may provide for improved vectorisation strategies but uptake by the liver and spleen seriously limits interaction with the target tissues and may therapeutic efficacy [54].

The great next step in nanodelivery for inorganic metal complexes is to combine intrinsic properties towards effective combinatory strategies to improve efficacy and reduce the dose dependant toxicity of chemicals. Another avenue of development is optimization of such systems for nanotheranostics, allowing disease progression monitorisation and therapeutic evaluation in real time [53,55]. Allowing a plan for each cancer treatment according to the patients individual responses, lowering the adverse side-effect and incorrect drug dosage would be some of the advantages of going nano.

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