Noble metals in oncology

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Worldwide research groups are searching for anticancer compounds, many of them are organometalic complexes having platinum group metals as their active centers. Most commonly used cytostatics from this group are cisplatin, carboplatin and oxaliplatin. Cisplatin was used fot the first time in 1978, from this time many platinum derivatives were created. In this review we present biological properties and probable future clinical use of platinum, gold, silver, iridium and ruthenium derivatives. Gold derivative Auranofin has been studied extensively. Action of silver nanoparticles on different cell lines was analysed. Iridium isotopes are commonly used in brachyterapy. Ruthenium compound new anti-tumour metastasis inhibitor (NAMI-A) is used in managing lung cancer metastases. Electroporation of another ruthenium based compound KP1339 was also studied. Most of described complexes have antiproliferative and proapoptotic properties. Further studies need to be made. Nevertheless noble metal based chemotherapeutics and compounds seem to be an interesting direction of research.

Key words: noble metals, platinum, gold, silver.

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Introduction

Platinum, ruthenium, rhodium, and iridium (platinum group metals) and gold together with silver (copper group metals) are known as noble metals. They have quite low chemical reactivity compared to other elements.

In this review we discuss the ones that are already used in oncology or have a therapeutic potential.

Platinum

Platinum (Pt), with atomic number 78, atomic mass 195.08, density 21.45 g/cm^3, and melting point 1772°C, is quite rare in nature and usually is found together with ruthenium, rhodium, and palladium. In chemical compounds it is mainly found in its oxygenation state of II, III, IV, and VI; it has very good properties of electric and thermal conductivity. Platinum was first found in Columbia in 1735, named from the Spanish "platinum", meaning "small silver" because of its relative lack of usefulness compared to silver, which is called in Spanish "plata". Platinum is mined in Russia, in the Republic of South Africa, Canada, and in the USA. Platinum is used in jewellery, stomatology, and in the motor industry. It is also used broadly in medicine.

Rosenberg *et al*. [1] used cisplatin firstly for the suppression of *Escherichia coli* growth. Platinum-based derivatives have found their way to be chemotherapeutics in cancer treatment. The most commonly used cytostatics from this group are cisplatin, carboplatin, and oxaliplatin (used from 1978, 1980, and 1988, respectively). They are used in the therapy of many malignant tumours: ovarian cancer, testicular cancer, lung cancer, oesophageal cancer, stomach cancer, prostate cancer, bladder cancer, squamous cell carcinoma of head and neck, cervical cancer combined with radiotherapy, colorectal cancer and non-Hodgkin lymphoma, multiple myeloma, neuroblastoma, melanoma, and mesothelioma [2].

Cisplatin is built from one atom of platinum, two chloride ions, and two molecules of ammonia. Carboplatin has one atom of platinum, two molecules of ammonia, and a cyclobutanedicarboxyl ligand with oxygen atom from the carboxyl group. Oxaliplatin, however, is a complex compound of platinum with 1,2-diaminocyclohexane and an oxalate group [3]. The addition of new ligands to platinum atom has been done with the aim of breaking chemoresistance to platinum compounds, which is observed during therapy. The search for platinum derivatives is linked to the increase of treatment efficacy. This may be a result of the quantity and type of new DNA adducts and also of the reduction of treatment side effects [4, 5].

Cytostatics that are platinum derivatives are alkylating agents. By making stable cross bindings with DNA (bonds with nucleophilic nitrogen atom N7 of two neighbouring guanines) DNA replication is blocked and cell apoptosis is induced. The cell cycle is blocked in the G2 phase. The change of DNA structure is recognised by specific proteins, including the hMSH2 protein form

the High Mobility Group (HMG), and may cause damage repair; other proteins may be a signal triggering apoptosis [6–9]. Gong *et al*. [10] found that cisplatin may also induce cell death in parallel by activation of suppressor protein p53 and protein p73. Neoplasms with p53 deficit are resistant to cisplatin treatment. There is, however, evidence that there are other (independent from p53 cell death) pathways in cisplatin based therapies. Cisplatin induces activation of the c-Abl tyrosine kinase, which may induce proapoptotic protein p73 [11–14].

According to the information enclosed with the drug, the most common side effects (more than 1 out of 10 patients) after cisplatin treatment are: leukopenia, thrombocytopenia, anaemia, hypernatremia, impairment of hearing, decreased appetite, nausea, diarrhoea, kidney malfunction, and fever. In more than 1 out of 100 patients but in less than 1 out of 10 patients peripheral neuropathy is observed, especially when cisplatin is combined with taxanes. Side effects of carboplatin include kidney damage (less often than cisplatin), alopecia, fatigue, and elevated liver enzyme activity. Oxaliplatin causes peripheral neuropathy, fatigue, hypernatraemia and hypokalaemia, anaemia, thrombocytopaenia, and leukopaenia.

Platinum derivatives play an important role in oncology. Use of platinum derivatives both in monotherapy and combination therapy can effectively cure cancer.

Gold

Gold (Au), with atomic number 79, atomic mass 197.0, density 19.3 g/cm^3, and melting point 1063^{o}C, is found in its free state and in minerals. In chemical compounds it is mainly in oxygenation states I and III; it has very good properties of electric and thermal conductivity.

The history of gold mining is more than 6000 years old, its colour and timeless value were well known in art and architecture of ancient civilisations. The main producer of gold is the Republic of South Africa, although it is also mined in other regions of the world.

Gold was used in medical fields from ancient times. Its complex auranofin is used in rheumatism treatment, and its anticancer potential is also described in both *in vitro* and *in vivo* models [15–17].

In recent years nanotechnology using structures of 1 nm to 150 nm also involves the use of gold. Nanotechnology is used in immunohistochemistry and gene therapy. Gold particles are stable and non-toxic; they can bind drugs, antibodies, or antigens, they can have transport and active substance release capability. They can also distribute substances to specific body parts or organs. They are safe for healthy tissues because they do not disintegrate during transport [15, 18, 19].

Numerous studies show that gold complexes have antiproliferative and proapoptotic properties. They reduce tumour mass also in platinum-resistant cancers, and they have lower toxicity, especially for the kidneys [20–22].

The anticancer activity of gold complexes is not known, although some research shows that they may have inhibiting activity towards enzymatic protein complexes like thioredoxin (Trx) and thioredoxin reductase (TrxR); they may also inhibit proteasome activity – a mechanism linked with carcinogenesis [15, 23–27].

Thioredoxin and thioredoxin reductase protect the cell from reactive oxygen species and apoptosis, and they are involved in cell growth and proliferation. Expression of thioredoxin is increased in many malignant carcinomas – it is one of the factors that is linked to cell chemoresistance; it is also linked to cells' invasive and metastatic potential. Thioredoxin also causes expression of hypoxia-induced factor 1 (HIF-1α) and increases production of protein products from the VEGF gene promoting neoangiogenesis in tumours [15, 28, 29].

Thioredoxin and thioredoxin reductase are found in two forms: cytoplasmic and mitochondrial (TrxR1 and TrxR2).

Gold complexes inhibit thioredoxin reductase in mitochondria by reducing membrane potential, leading to apoptosis [15, 21]. It is thought that the enzymatic complex of thioredoxin – thioredoxin reductase can be a target in cancer therapy [26, 28].

Another anticancer mechanism of gold is inhibition of the proteasome complex. This is a complex responsible for degradation of ubiquitin marked proteins that may cause selective apoptosis of cancer cells [16, 20].

Gold complexes are also responsible for telomerase and STAT pathway inhibition. STAT pathway is a transcription activator that plays a role in proliferation and has an antiapoptotic effect on cancer cells [30].

Recent research has shown evidence anticancer activity of gold complexes both *in vitro* and *in vivo*. It was proven that auranofin in human ovarian cancer cell lines induces apoptosis by inhibition of thioredoxin reductase; it was also proven on cisplatin-resistant cell lines [21]. A similar action of gold (III) complex was observed on human ovarian cancer stem lines, and in one study it was compared with cisplatin and oxaliplatin. Antiproliferative and proapoptotic actions of gold complexes were stronger than those of platinum derivatives [22]. In another study gold complexes were assessed for their antiproliferative potential in ovarian cancer cell lines and embryonic cell lines – it was found that they selectively inhibit thioredoxin reductase in cancer cells [24].

A study on human breast cancer showed that the use of auranofin also has an anticancer effect; the inhibition mechanism was linked to the STAT pathway and telomerase [30]. It was found that the effectiveness of pegylated gold nanoparticles (AUNPs) combined with docetaxel on prostate cancer cell lines was 50% – only half of cells survived, others were damaged [31]. An even higher effectiveness of gold nanoparticles was observed in xenograft of human prostate cancer in mice with the use of particles having gold Au^{198} isotope [32].

Gold nanoparticle complex was developed, and this complex was linked to the cetuximab antibody and gemcitabine, which was administered to animals that had hepatocellular carcinoma (HCC) heterografts. Heterografts entered apoptotic pathway, they were found to be necrotic, their proliferative potential was diminished, and healthy tissues were not damaged [33].

An interesting study on auranofin use in transgenic mice with chronic lymphocytic leukaemia (CLL) was made. This type of leukaemia has a high remission rate after

first-line chemotherapy, although relapses are linked to chemoresistance. Auranofin has been seen to reduce tumour size, extending overall survival [34].

It seems that gold complexes and nanoparticles, because of their anticancer activity, will find their way into clinical trials, not only experimental models.

Silver

Silver (Ag, lat. *argentum*), with atomic number 47, atomic mass 107.86, density 10490 kg/m^3, and melting point 961.78°C, is found in nature in its free state and in minerals like argentite. It is a silver-white metal, with very good thermal and electrical conductivity. Silver was mined for the first time in 2500 BC in Asia Minor.

Silver was known for its antibacterial properties in ancient times. Greeks coated plates and cups with silver to stop disease spreading, and they put silver coins into water buckets to extend the water's freshness. They also gave silver spoons to children for sucking, which was believed to protect them from illnesses. The very first silver compound that was used for treatment was silver nitrate, which was discovered by Basilius Valentinus back in the 15th century [35].

In the 19th century, for the first time, 0.2% solution of silver nitrate was used for burn wound care. In 1874 T. Billroth proved the antiseptic properties of silver by using its antibacterial effect on *Staphylococcus aureus*. Later on the antibacterial properties of silver were proven against the following bacteria: *Streptococcus, Pseudomonas* and *Escherichia* [36]. In the early 1990s it was observed that people with low concentrations of silver as a trace element often undergo bacterial, viral, or fungal infections [37]. Nowadays many surgical instruments are silver coated, as well as other instruments like dialysis catheters. Everywhere where risk of infection is present, silver can be used.

In the last few years oncological research was dominated by nanoparticles, some of which included silver. The first report of the cytotoxic effect of silver nanoparticles (AgNPs) was proven against MCF-7 breast cancer cell line in 2013 [38]. Researchers developed silver nanoparticle synthesis with the use of plant extracts. Kathiravan [39] used the extract of *Melia dubia* leaves (a tree growing in India), and Sathishkumar [40] used extract from *Dendrophthoe falcata*. Silver nanoparticles developed in this way were proven to have an anticarcinogenic effect on MCF-7 breast cancer cell line. Vasanth [41], with the use of AgNPs, stopped replication of a cervical cancer cell line (HeLA) by induction of apoptosis. To produce silver nanoparticles he used extract from the bark of *Moringa oleifera*. Chinese researchers have proven the cytotoxic effect of silver nanoparticles against AML (acute myeloid leukaemia) cell lines such as SHI-1, THP-1, DAMI. This effect was greater against those cells than against normal hematopoietic cells [42]. Yu-Len Li [43] investigated three mononuclear complexes with quinoline. He proved that those complexes inhibit proliferation by inducing cell cycle cessation in phase G1 and S in hepatocellular carcinoma cell line (HepG2). Lacatelii [44] investigated the *glioblastoma* cell line (U87MG). He observed *in vivo* tumour reduction when a silver nanoparticle was combined with alisertib (selective kinase inhibitor).

Therapy with silver nanoparticles is an alternative to conventional chemotherapy. Current research on those nanoparticles looks very promising, but further investigation is needed.

Iridium

Iridium (Ir), with atomic number 77, atomic mass 192.217, density 22.56 g/cm^3, and melting point 2466°C, is found in nature as osmiridium (an alloy of osmium and iridium). In chemical compounds it is mainly in an oxygenation state of IV; oxygenation states II, III, and VI are also possible, and it has good properties of electric and thermal conductivity.

Discovered in 1803 by Smithson Tennant, iridium belongs to the platinum group. Iridium was named after the greek rainbow goddess Iris because of its different coloured salts. It is one of the most dense and least reactive elements in nature. Annual production of iridium is only 3 tonnes; it is one of the rarest elements in nature. At easily creates complex compounds.

Until now, in areas linked to medicine, iridium has been used together with platinum as a component of electrodes for stimulation [45]. Iridium oxide was used instead of Ag/AgCl in dry electrodes with microtips that could be used without gel EEG [46]. Because of the high price of iridium there was an attempt to produce electrodes with titanium-iridium oxide [47].

In oncology iridium has found its way as Ir^{192} isotope in brachytherapy. Its half-life is only 74 days. Iridium sources are small and thin. They can be used in after-loading systems that protect medical staff from radiation. It is one of the basic isotopes used in brachytherapy. In the field of gynaecological oncology it is used mainly in plesiobrachytheraphy in cervical and uterine cancer [48, 49].

Research was made on the use of iridium in Flt4 (also known as VEGFR3) kinase inhibitor [50, 51].

Ruthenium

Ruthenium (Ru), with atomic number 44, atomic mass 101.07, density 12.45 g/cm^3, and melting point 2334°C, is found in nature as sulphide, iron, and chrome ores. In chemical compounds it is mainly in oxygenation state IV. Oxygenation states II, III, VI, and VIII are also possible. Annual mining of ruthenium is only 20 tonnes. Some researchers claim that ruthenium was first discovered in 1808 by Jędrzej Śniadecki; he called this element vestium in honour of the discovery of the planet Vesta [52].

The first ruthenium compound used in clinical practice was NAMI-A. It was proven to be effective in managing lung cancer metastases. Currently NAMI-A is used together with gemcitabine as second-line chemotherapy in the treatment of metastases in non-small cell lung carcinoma [53].

Other compounds used in clinical practice are KP1019, and soluble salt KP1339, which has finished phase I of a clinical trial in neuroendocrine carcinomas [54]. Electroporation of KP1339 was tested in Slovenia, and this meth-

od was found to be effective *in vivo* because of its extra antiangiogenic properties. It may also spread the idea of electrochemotherapy, which is based on local injection of chemotherapeutics accompanied by electrical impulses [55].

Ruthenium was also used in photodynamic therapy [56, 57]. Nanocompounds based on ruthenium derivatives have been developed. Mangiapia *et al*. developed DoHuRu, HoThyRu, and ToThyRu, which are AziRu derivatives, and together with phospholipids they created stable nanoaggregates. The antiproliferative activity of nanocompounds towards cell lines WiDr, C6, and MCF-7 was also studied [58].

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