Modulatory effects of Ruthenium(II)-based complexes on oxidative stress induced by activated HL60 cells and Neutrophils

Collienne S[1,2], Franck T[1,3], Delaude L[4],Vaesen F[1], Mormoen J[1], Hoebeke M[1,2], Serteyn D[1,3], Mouithys-Mickalad A[1].

[1] Centre for Oxygen, R&D (CORD), Institute of Chemistry, B6a. [2] Laboratory of Biomedical Spectroscopy, Department of Physics, Institute of Physics B5a. [3] Equine Clinic, Faculty of Veterinary Medicine. [4] Laboratory of Organometallic Chemistry and Homogeneous Catalysis, Institute of Chemistry, B6a, University of Liège, B-4000 Liège, Belgium.

There is a growing interest in the use of metal-based chemotherapeutic agents to fight different types of cancers [1]. Among the most commonly used family of organometallic compounds derived from platinum, Cisplatin (CisPt) is the lead compound for the treatment of various cancers including lung, testis, gastric, breast, etc. Nevertheless, beside its recognized therapeutic effects, side effects such as gastric toxicity and acute kidney failure were observed during treatment with CisPt, thereby limiting its clinical use. Other compounds are currently studied and among them, Ruthenium (Ru) complexes have gained more importance for their lower toxicity and aggressive effect on healthy tissues than CisPt. Ru-complexes are also more resorbed and excreted [2]. Numerous studies focused on the mechanisms of action of Ruthenium compounds to fight cancer, including antioxidant or pro-oxidant activity.

During inflammation, activation and infiltration of neutrophils contribute to oxidant stress playing a crucial role in tumor development. Likewise, the degranulation of neutrophil causes the release of myeloperoxidase (MPO), which reacts with H_2O_2 to catalyze redox reactions. A therapeutic target to control inflammation is the modulation of oxidant enzymes and cells involved in radical species production and redox reactions.

Because Ruthenium compounds can easily enter into cancer cells, a series of newly synthesized Ru(II)-complexes were used for this purpose. They were first tested for their radical scavenging activities using ABTS and 1,1-diphenyl-2-picrylhydrazyl (DPPH) assays.

Amongst them, compound **1** (LD0436) and compound **2** (LD04037) were then studied for their ability to modulate the reactive oxygen species (ROS) production by inflammatory cells like human promyelocytic leukemia cell line (HL 60) and neutrophils (PMN) using fluorescence, chemiluminescence (CL) and electron spin resonance (ESR) techniques. The toxicity of those Ru-complexes against HL-60 and neutrophils was checked using Trypan blue exclusion assay.

Altogether, CL and ESR findings indicate that both complexes **1** (LD0436) and **2** (LD0437) exhibit a dose-dependent inhibitory activity compared to CisPt, gallic acid, curcumin and quercetin, which were taken as reference molecules in the various systems investigated. Similarly, the Ru(II) complexes tested also display an antioxidant profile on the substrate oxidation catalyzed by peroxidase such as MPO mainly involved in acute and chronic inflammatory situations.

1: (RuCl(*p*-cymene)(S_2C.IDip)]$^+$(PF_6)$^-$], **2**: (RuCl(*p*-cymene)(S_2C.ICy)]$^+$(PF_6)$^-$]

References:

1. Ceresa C, Brawin A, Cavaletti G, Trinidad A et al., (2014) Current Medicinal Chemistry 20(21), 2237-2265.
2. Liu, Y, Zhang X, Zhang R, et al., (2011) European Journal of Inorganic Chemistry. 1974-1980.