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A B S T R A C T

Introduction/Justification: Melanoma is the most aggressive type of skin cancer, with increasing global incidence. Platinum-based chemotherapy, particularly cisplatin, remains a standard treatment, but its effectiveness is often limited by drug resistance and severe side effects. Gold-based complexes have gained attention as potential alternatives due to their greater chemical stability, selective cytotoxicity against platinum-resistant cells, lower systemic toxicity, and immunomodulatory effects. Previous studies from our group demonstrated the antiproliferative activity of AuDMAP, a gold(I)-based complex, in the UACC-62 melanoma cell line. Building on these findings, this study investigates the antiproliferative effects, cytotoxicity, and selectivity of AuDMAP in SK-MEL-28 and A-375 melanoma cells, as well as its impact on cell migration and potential anti-metastatic properties in comparison to cisplatin. **Objectives:** To evaluate the antiproliferative activity and cell death mechanisms induced by the AuDMAP complex in SK-MEL-28 and A-375 melanoma cell lines, as well as determining its toxicity against non-tumoral HaCaT cells. **Materials and Methods:** Melanoma and non-tumor cells were cultured in DMEM + 10% FBS + 1% penicillin-streptomycin and treated with AuDMAP (0.78–100 μM) for 48h, with cisplatin as a control. Sulforhodamine B (SRB) and Thiazolyl Blue Tetrazolium Bromide (MTT) assays were performed to determine cell viability, antiproliferative activity, and IC50 values. The wound healing assay assessed migration, and flow cytometry will be conducted to explore cell death mechanisms and cell cycle effects. **Results:** AuDMAP exhibited strong antiproliferative activity, inhibiting ~80% of cell proliferation at 6.25 μM in melanoma cells - 15x more effective than cisplatin for SK-MEL-28 and 3.3x for A-375. IC50 values were 2.61 μM (SK-MEL-28), 2.50 μM (A-375), and 1.81 μM (HaCaT), yielding a low Selectivity Index (0.69–0.72). Migration assays revealed that AuDMAP significantly reduced wound closure, suggesting anti-metastatic potential. In A-375, wound closure was -8.5% with AuDMAP vs. 62.8% with cisplatin (6.25 μM), while in SK-MEL-28, closure was 4.6% vs. -13.5%, respectively. Given these promising results, further studies will focus on cell cycle analysis and death mechanisms to better understand the biological effects of AuDMAP. **Conclusion:** AuDMAP is a gold(I)-based complex that demonstrates potent antiproliferative and antimigratory effects in melanoma cells, with efficacy significantly superior to cisplatin in the tested models. The inhibition of cell proliferation and migration suggests its potential as a promising anticancer agent, possibly disrupting tumor progression and metastasis. However, the low selectivity index observed indicates that its cytotoxic effects extend to non-tumor cells, raising concerns about the safety profile in intravenous administration. To further explore its therapeutic viability, future studies will investigate its mechanisms of action at the molecular level, focusing on cell cycle modulation and programmed cell death pathways. These findings contribute to the growing interest in gold(I) compounds as novel candidates for melanoma treatment, particularly for topical administration. **Acknowledgements:** This study was supported by grants from the Brazilian Agencies FAPESP (2021/10265-8 Cancer Theranostics Innovation Center - CEPID), and Program (PPPD) at the University of Campinas (UNICAMP, ID Number 325141).

Keywords: AuDMAP, Cell proliferation, Melanoma, Skin cancer.

https://doi.org/10.1016/j.htct.2025.103765

EVALUATION OF ANTIPROLIFERATIVE OF A POTENTIAL THERAPEUTIC ASSOCIATION OF SILVER COMPLEXES WITH LIMONENE IN SQUAMOUS CELL CARCINOMA AND MELANOMA CELL LINES

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A B S T R A C T

Introduction/Justification: Skin cancer, strongly associated with UV exposure, is the most common malignancy worldwide, including squamous cell carcinoma (SCC), and cutaneous melanoma (CM). Although cisplatin and 5-FU are standard treatments for SCC and CM, the development of new therapeutic alternatives is crucial. Silver complexes have shown promising anticancer potential, while the monoterpene limonene has demonstrated efficacy in enhancing skin permeation, supporting its application in topical drug delivery. **Objectives:** Our study aimed to evaluate the in vitro antiproliferative effects of silver complexes and limonene, isolated and in association. **Materials and Methods:** The silver complexes identified as I and II were synthesized at the Institute of Chemistry of University of Campinas. The pure substances R-(+)-limonene and S-(-)-limonene were acquired from Merck. Pharyngeal SCC (FaDU) and melanoma (A-375, SK-MEL-28) cells (4×10^3 cells/mL) were treated with complexes I e II (0.4–400 μM) or their combination with R-(+) and S-(-) limonene (4 μM). Cisplatin and 5-FU (100 μL/well, 0.4 to 400 μg/mL, in triplicate) were used as positive controls. Before (T0) and after (T1) sample addition, cells were fixed with 50% trichloroacetic acid (TCA, 50 μL/well), and were then resuspended in Tris base for subsequent absorbance at 540 nm with a microplate reader spectrophotometer (VersaMax, Molecular Devices). The difference between T0 and T1 absorbance values represented 100% cell growth. Effective concentration representing the sample concentration required to

promote 50% growth inhibition (IC50) for each cell line was calculated by sigmoidal regression using Origin 8.0 software. The Combination Reduction Index (CRI) was calculated as IC 50 of the metal complex + monoterpene / IC 50 of the metal complex alone. **Results:** Both silver complexes exhibited potent antiproliferative activity. The antiproliferative effect of silver complex I ranged from 4 μM to 10 μM in SCC and CM cell lines, whereas the antiproliferative effect of silver complex II ranged from 1 μM to 6 μM in the same cell lines. The association of silver complex I in combination with S-(-)-limonene resulted in synergism effect in the FaDu cell line with IC50 < 2 μM, CRI = 0.4. The association of silver complex II with both enantiomers demonstrated a partial synergistic effect in the FaDu and SK-MEL-28 cells, with IC50 <1.5 μM and CRI = 0.5. **Conclusion:** Silver complexes are promising candidates for in vivo studies as potential alternatives for the treatment of patients with SCC and CM. Additional experiments are necessary to evaluate their mechanism of action and toxicity. The study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Apoio ao Ensino e à Pesquisa do Estado de São Paulo (FAPESP #2016/07729-4; #2023/09738-4 and Cancer Theranostics Innovation Center, (CancerThera), CEPID FAPESP #2021/10265-8).

Keywords: Combination, Limonene, Melanoma, Silver complexes, Squamous cell carcinoma.

https://doi.org/10.1016/j.htct.2025.103766

ROLE OF GENETIC VARIABILITY IN METABOLIC PATHWAYS ON CISPLATIN-INDUCED KIDNEY INJURY IN HEAD AND NECK CANCER PATIENTS

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A B S T R A C T

Introduction/Justification: Head and neck squamous cell carcinoma (HNSCC) is a prevalent malignancy responsible for approximately 5.0% of global cancer deaths. The standard treatment for locally advanced HNSCC involves cisplatin (CDDP)-based chemotherapy and radiotherapy, which can lead to significant adverse effects, particularly nephrotoxicity. It is already well known that the efficacy of CDDP as well as its side effects vary in distinct patients with HNSCC, and single nucleotide variants (SNVs) in genes that act in CDDP metabolism constitute a plausible explanation for this finding. **Objectives:** To investigate the roles of SNVs GSTM1, GSTT1, GSTP1 c.313A>G, XPC c.2815A>C, XPD c.934G>A and c.2251A>C, XPF c.2505T>C, ERCC1 c.354C>T, MLH1 c.93G>A, MSH2 c.211+9C>G, MSH3 c.3133A>G, EXO1 c.1765G>A, TP53 c.215G>C, CASP3 c.-1191A>G and c.-182-247G>T, FAS c.-1378G>A and c.-671A>G, and FASL c.-844C>T SNVs on kidney function outcomes in HNSCC patients undergoing CDDP treatment. **Materials and Methods:** A total of 109 patients with locally advanced HNSCC treated with CDDP were included in the study. Genotypes were determined using polymerase chain reaction (PCR). Renal function was assessed by calculating estimating glomerular filtration rate (eGFR) using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, before treatment initiation and 30 days post-treatment. The percentage variation in kidney function was calculated by determining the difference between baseline (pre-chemotherapy) and follow-up (post-chemotherapy) values for eGFR divided by the pre-chemotherapy value and represented as ΔeGFR. **Results:** Patients with the GSTT1 present and ERCC1 c.354CT or TT isolated genotypes presented a decline in kidney function of 4.94% and 8.94%, respectively. A decline of 17.67% in renal function post-CDDP treatment was observed in patients with the GSTT1 present combined with TP53 c.215CC genotype. Patients with the GSTP1 c.313AG or GG and ERCC1 c.354CT or TTC>T (17.57%), MLH1 c.93GA or A (12.49%), or MSH3 c.3133AG or GG (12.19%) combined genotypes showed a reduction in renal function after CDDP treatment. Renal function declines of 18.85% and 13.38% were observed in patients with ERCC1 c.354CT or TT and MLH1 c.93GA or AA or MSH3 c.3133AG or GG combined genotypes, respectively. **Conclusion:** Our data indicates, for the first time, preliminary evidence that combined inherited abnormalities, SNVs that act in CDDP metabolism, act as independent factors for nephrotoxicity in HNSCC patients and can be used to select patients for personalized treatments that promote renal protection and reduced nephrotoxicity. **Acknowledgements:** The study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (grant number 88887.513947/2020-00), the Postdoctoral Program (PPPD) at the University of Campinas (UNICAMP) (Postdoctoral ID number: 326285), and the Fundação de Apoio ao Ensino e à Pesquisa do Estado de São Paulo (FAPESP) Cancer Theranostics Innovation Center (CancerThera) (FAPESP 2021/10265-8).

Keywords: Cisplatin, Head and neck squamous cell carcinoma, Nephrotoxicity, Single nucleotide variants.

https://doi.org/10.1016/j.htct.2025.103767

KIF13B C.*3163G>A SINGLE NUCLEOTIDE VARIANT ON OROPHARYNGEAL SQUAMOUS CELL CARCINOMA SUSCEPTIBILITY AND TUMOR CHARACTERISTICS

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