PROTOCOL OF A RANDOMIZED PILOT STUDY ON SURVIVAL IN NEWLY DIAGNOSED GLIOBLASTOMA PATIENTS UNDERGOING CHEMORADIATION VERSUS COMBINED CHEMORADIATION WITH INTRANASAL PERILLYL ALCOHOL

DANIELA CARNEIRO DE Lima [a],
Alex H. Schöntal [b],
Clóvis Orlando Pereira da Fonseca [c],
Fabiano Reis [d], Carmen Silva Passos Lima [d],
Mary Ann Foglio [a]

[a] *Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil*
[b] *University of Southern California, Los Angeles, United States*
[c] *Hospital Federal de Ipanema, Ipanema, RJ, Brazil*
[d] *Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil*

A B S T R A C T

Introduction/Justification: Glioblastoma multiforme (GBM) is a highly aggressive type of brain tumor and remains one of the most challenging cancers to treat. This tumor is characterized by rapid progression and unfavorable prognosis. After undergoing surgery, radiotherapy (RT), and chemotherapy (CT) with temozolomide (TMZ), patients generally exhibit low survival rates. Perillyl alcohol (POH) is a hydroxylated monoterpene with antitumor, anti-angiogenic, and pro-apoptotic properties, inhibiting RAS oncogene-mediated signaling. In vitro and in vivo studies showed POH's cytotoxicity to both TMZ-resistant and sensitive cells, and its effectiveness as a radiosensitizer in malignant glioma cell lines. In phase I/II trials with oral POH in advanced, refractory cancer patients, nausea and other gastrointestinal toxicities led to study discontinuation. Currently, POH is being studied as an inhaled anticancer agent, showing no toxicity and promising activity with increased survival in patients with recurrent gliomas, however, these studies were not randomized, and to date, these investigations have been conducted exclusively in patients with recurrent gliomas. **Objectives:** This study presents a protocol from the University of Campinas, developed by experts across multiple fields, to evaluate the effects of intranasal POH in GBM patients. **Materials and Methods:** Patient's will be recruited from the Oncology Service at the General Hospital of the University of Campinas (UNICAMP) after tumor resection, with a total of 40 participants. Adult individuals of any gender will be included. Through randomization, participants will be randomly assigned to two groups: the control group (RT+CT) and the intervention group (RT+CT + POH inhalations). Block randomization of four patients will ensure balance between groups during recruitment. The randomization sequence was generated at www.randomization.com. The control group will undergo RT and CT with TMZ: 75 mg/m^2 of TMZ daily for 6 weeks during RT (2 Gy/day for 5 days a week, totaling 60 Gy), followed by 150 or 200 mg/m^2 of TMZ for 5 days per cycle in 28-day cycles for 6 cycles. The participants in the intervention group will receive the same treatment plus 0.3% POH inhalations (55 mg in 3 mL of water, 4 times daily, with 6-hour intervals). They will undergo 6 weeks of RT + TMZ + POH, followed by 6 cycles of TMZ + POH (5 days of TMZ + POH, followed by 23 days of POH only). Cranial MRIs will be analyzed by an expert neuroradiologist using T2/FLAIR signal intensity with perfusion, without knowledge of patient group allocation. MRIs are part of routine treatment, performed every 3-4 months in the first year, and response will be assessed using MacDonald and RANO criteria for high-grade gliomas. Toxicity assessment of standard treatment with POH will follow the NCI Common Terminology Criteria, version 5.0. Progression-free survival will be compared between patients receiving only RT and CT and those also undergoing POH inhalation, with survival curves calculated using the Kaplan-Meier method. **Results:** *Perspectives:* Patients in the intervention group are expected to have higher survival rates, indicating a benefit of intranasal POH with standard treatment. **Conclusion:** *Acknowledgement:* The study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Keywords: Glioblastoma, Perillyl alcohol, Protocol.

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ANTIPROLIFERATIVE ACTIVITIES IN VITRO OVER SQUAMOUS CELL CARCINOMAS OF A PALLADIUM(II) COMPLEX WITH AMANTADINE

Pedro Corbi, Laura Barros Silva,
Fernanda Van Petten V. Azevedo,
Gilberto C. Franchi Jr, Carmen Silvia P. Lima

Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

A B S T R A C T

Introduction/Justification: Metal-based drugs have been used in diagnosis and treatment of different types of cancer since the discovery of cisplatin's antineoplastic properties in the 1960's. Second-generation drugs based on the platinum(II) complex cisplatin, such as carboplatin and oxaliplatin, were developed and used for cancer treatment worldwide. However, platinum(II) drugs typically cause side effects, such as nephrotoxicity, neurotoxicity and myelosuppression, which motivates the search for new drug candidates. Since the platinum(II) and palladium(II) ions have similar characteristics and form analogous compounds, palladium(II) complexes have been also studied as potential anticancer agents. Recently, a new palladium(II) drug named padeliporfin (Tookad® Soluble) has entered the clinic for the treatment of low-risk prostate cancer, which further motivates the investigation of palladium(II) complexes as potential antineoplastic drugs. Adamantanes are a class of organic compounds that consist of a single diamond-like carbon cage. The functionalization of adamantane with an amine group lead to amantadine, which has been used in the clinic as an antiviral and

anti-Parkinson drug and has also been evaluated for its anticancer activity. **Objectives:** In this study, we report for the first time the antiproliferative studies of a palladium(II) complex with amantadine (Pd-atd) over squamous cell carcinomas **Materials and Methods:** The Pd-atd complex was prepared following the literature protocol. Briefly, the complex was prepared by the reaction of Li2PdCl4 with amantadine hydrochloride in methanol under stirring and at room temperature. The yellowish solid obtained was collected by filtration, washed with methanol and dried. Yield 72%. The [PdCl2(C10H17N)2] composition was confirmed by chemical and spectroscopic analyses. Squamous cell carcinoma of tongue (SCC-4 and SCC-25) and of hypopharynx (Fadu), and a non-tumoral cell line (HaCat, immortalized keratinocyte) were used in this study. Cells were cultivated following the methodology previously described in the literature. Cell viability was determined by dose-response curves obtained from an MTT assay measuring the absorbance after 48h. **Results:** The Pd-atd complex inhibited proliferation of SCC-4 cells with an IC50 of 1.87 μM and it was non-toxic to HaCat cells. Cisplatin, a standard drug, presented an IC50 of 7.02 μM and it was less selective toward HaCat cells in the same experimental conditions. **Conclusion:** The promising results of the antiproliferative activities of the Pd-atd complex over SCC-4 cells warrant for additional studies about the potential of application of the complex as an antiproliferative agent for the treatment of squamous cell carcinomas. **Acknowledgements:** This study was supported by grants from the Brazilian Agencies FAPESP (2022/08320-3 and 2021/10265-8 Cancer Theranostics Innovation Center - CEPID), CNPq (309800/2021-8) and Program PPPD at the University of Campinas-UNICAMP (ID number 325141).

Keywords: Aminoadamantane, Antiproliferative agent, Palladium(II), Squamous cell carcinoma.

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EFEITO DA ATIVAÇÃO NEUTRÔNICA NO COPOLÍMERO PLA-PEG ASSOCIADO À NANOPARTÍCULAS DE OURO

Samara Mendes Matos,
Nathali Ricardo Barbosa de Lima,
Luciana Carvalheira

Instituto de Engenharia Nuclear, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil

R E S U M O

Introdução/Justificativa: Nos últimos anos, vários estudos têm sido dedicados à compreensão dos efeitos da radiação ionizante sobre moléculas orgânicas, especialmente aquelas com potencial para aplicações médicas e farmacológicas. Devido à sua variedade, versatilidade e propriedades, os materiais poliméricos são a classe de materiais mais investigada no desenvolvimento de sistemas para aplicação na medicina. O polietilenoglicol (PEG) é um polímero quimicamente estável, regularmente utilizado em cosméticos e como carga em produtos farmacêuticos, pois o organismo o elimina sem metabolizá-lo. Além disso, as partículas de PEG escapam do reconhecimento e captura por células fagocíticas após a administração in vivo, permanecendo por um período prolongado na circulação sistêmica. Já o ácido polilático (PLA) é um poliéster alifático biocompatível e biodegradável, sintetizado a partir de recursos renováveis, como amido de milho ou cana-de-açúcar. Devido às sua taxa de degradação lenta e baixa toxicidade, o PLA tem sido amplamente utilizado em sistemas de liberação de fármacos. A combinação de PEG e PLA como copolímero (PLA-PEG) oferece um efeito sinérgico ao combinar a hidrofilicidade do PEG com a biodegradabilidade do PLA. O uso deste copolímero na área médica tem ocorrido de diversas formas, sendo de interesse principal estudar sua associação com nanopartículas de ouro (AuNPs) e a aplicação desses nanossistemas tanto para exames de imagem quanto para terapia. A utilização do copolímero PLA-PEG para a funcionalização superficial das AuNPs pode otimizar ainda mais o desempenho deste nanossistema, melhorando a estabilidade e permitindo um encapsulamento e liberação mais eficiente dos fármacos de interesse. A alta energia emitida por fontes radioativas causa a formação de radicais livres que podem se recombinar, levando a um rearranjo das cadeias poliméricas. Esse processo pode resultar em reticulação ou degradação do material irradiado. **Objetivos:** O objetivo deste estudo é avaliar os efeitos da ativação neutrônica do complexo formado por AuNPs-SH-PEG-PLA, observando se ocorre radiólise desses polímeros ou alguma degradação nesse sistema. Este estudo também nos fornecerá informações sobre a dose mínima necessária para a ativação desse complexo, o que é de extrema importância não apenas para os pacientes, mas também para a proteção radiológica de todos os profissionais envolvidos no processo. **Materiais e Métodos:** A obtenção do nanossistema AuNPs-SH-PEG-PLA foi baseada na metodologia de Reena et al. (2017). O nanosistema foi irradiado no canal J9 com um fluxo de nêutrons de 10^8 n. $cm^{-2}.s^{-1}$ no reator Argonauta, com um tempo de irradiação de 2h para cada amostra. Foram obtidas 2 amostras, cada uma contendo uma alíquota de 3 ml do nanosistema. As amostras foram divididas de acordo com a dose aplicada, sendo que a primeira amostra não recebeu nenhum tipo de irradiação e as outras receberam 2,10 Gy. **Resultados:** Em função do estágio inicial da pesquisa, os resultados e suas respectivas análises estão em andamento, conforme o planejado. **Conclusão:** Mesmo com os estudos ainda em andamento, o revestimento de AuNPs com PEG-PLA desenvolvido neste estudo tem potencial para ser uma ferramenta útil para a obtenção de nanomateriais funcionalizados adequados para posterior ligação a fármacos com atividade antitumoral ou para uso como agentes de contraste em diagnóstico.

Palavras-chave: Ácido polilático, Argonauta, Nanopartículas de ouro, Polietilenoglicol, Polímeros.

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