DESCRIPTION OF THE RESEARCH, REASONS WHY THE RESEARCH TOPIC WAS UNDERTAKEN

According to WHO, the estimated prevalence of all cancers within a 5-year period worldwide exceeded 50.5 million cases in 2020. Chemotherapeutic agents efficiently kill cancer cells, but also cause severe side effects in non-target brain cells, leading to cognitive impairment. Over 90% of chemotherapy-treated patients report cognitive difficulties even after 5 years from treatment cessation. The most frequently used chemotherapeutic is **5-fluorouracil (5FU)** which, in addition to antineoplastic properties, appeared to decrease neurogenesis, impair myelination, and reduce neurotransmitter synthesis. There is a strong need to identify mechanisms of chemotherapy-induced toxicity to the brain cells and to find therapeutics that can effectively protect brain neurons and glial cells from 5FU-induced damage. **Proliferator-activated receptor gamma (PPARγ)** is currently considered a highly promising target in the treatment of neurodegenerations. Although activation of PPARγ appeared beneficial for brain cells, the utility of full PPARγ agonists such as anti-diabetic thiazolidinediones (TZDs) has been questioned due to hepatotoxicity and cardiotoxicity. **Here, we propose a new treatment strategy based on selective modulation of PPARγ with amorfrutin B to reduce chemotherapy-induced damage to neuronal and glial cells and to attenuate the related neuroinflammation.** Amorfrutin B is a **selective PPARγ modulator (SPPARγM)** devoid of side effects characteristic for TZDs. There is no report showing the protective capacity of SPPARγMs against chemotherapy-induced toxicity to the brain cells, which prompts us to investigate this research problem. A proof of concept for amorfrutin B-attributed neuroprotection has been recently published by our research group. Given the safe pharmacological profile of amorfrutin B, we anticipate that amorfrutin B will protect brain cells against 5FU-induced damage and related neuroinflammation. Furthermore, we expect that amorfrutin B will not compromise the antitumor efficacy of 5FU.

AIM OF THE PROJECT

The research hypothesis assumes that amorfrutin B does not interfere with or does potentiate the antineoplastic effects of 5FU and has the ability to inhibit both, 5FU-induced damage to the brain cells (neurons, oligodendrocytes), and microglia-dependent inflammatory response to 5FU. In this project, we aim to 1) Ensure that amorfrutin B does not impair the anticancer potential of 5FU. In fact, we expect that amorfrutin B will accelerate the anticancer effects of 5FU. 2) Assess the protective and anti-inflammatory potential of amorfrutin B in experimental models of 5FU-induced damage to neurons, oligodendrocytes and microglia. 3) Determine the molecular mechanisms of action of amorfrutin B in 5FU-treated brain cells.

EXPECTED RESULTS

All experiments will be carried out *in vitro* in human breast cancer cell line, mouse primary neuronal cells and/or human iPSCs-derived neurons, mouse primary oligodendrocytes and/or human iPSCs-derived oligodendrocytes, and microglia cell line. The protective potential of amorfrutin B will be assessed in respect to necrosis, apoptosis, autophagy, PPARγ-related pathways as well as neuroinflammation and epigenetic statuses. Treatment of chemotherapy-evoked side effects in non-malignant nervous system cells is a pressing issue, since chemotherapy evokes toxicity to neurons and glial cells, that finally results in chemotherapy-related cognitive impairment. The proposed amorfrutin B-based pharmacotherapy gives prospects for effective protection of brain cells against 5FU chemotherapy-induced side effects. We postulate, that the future treatment of chemotherapy-induced toxicity in the brain cells should target multiple cell populations, and those combined effects of amorfrutin B-based pharmacotherapy may then cause improvement in the cognitive and psychological well-being of patients.