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Polyphenols Inhibit the Pro-Apoptotic Effects of Methotrexate and 6-Mercaptopurine in Lymphoid and Myeloid Leukaemia Cells Lines

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Background: Anti-metabolite agents such as methotrexate and 6-mercaptopurine are widely used in the treatment of leukaemia and lymphoma. This study aimed to assess the effects of anti-metabolites when used in combination with polyphenols and determine whether polyphenols can sensitise leukaemia cells causing cell-cycle arrest, inhibition of cell proliferation and induction of apoptosis in response to methotrexate and 6-mercaptopurine. The rationale for the study is that some polyphenols have been shown to sensitize tumour cells from other tumour types to chemotherapy-induced apoptosis and/or cell cycle arrest, potentially allowing reduction of doses whilst maintaining efficacy.

Methods: Methotrexate and 6-mercaptopurine were investigated alone and in combination with five polyphenols (quercetin, apigenin, emodin, rhein or cis-stilbene) in two lymphoid (JURKAT and CCRF-CEM) and two myeloid (THP-1 and KG-1a) leukaemia cells lines. Measurements were made of ATP levels (CellTiter-Glo®assay), cell-cycle progression (propidium iodide (PI) staining and flow cytometry) and apoptosis (NucView-caspase-3 assay and Hoechst 33342/PI staining). The effects of these combinations on the apoptotic pathway (caspases-3, -8 and -9 Glo®luminescent assays), glutathione levels (GSH-Glo™-glutathione assay and cell tracker™ green-5-chloromethylfluorescein-diacetate-glutathione staining) and DNA damage (Alexa Fluor® 647 Mouse anti-H2AX staining) were also determined.

Results: Polyphenols, when combined with methotrexate or 6-mercaptopurine had an antagonistic effect, reversing chemotherapy-induced inhibition of ATP levels and induction of apoptosis, and had no effect on cell-cycle progression in either the lymphoid or myeloid leukaemia cell lines. Mechanistically the anti-metabolites/polyphenols combinations treatments significantly increased cell glutathione levels, and prevented the formation of γ-H2AX foci (a hallmark of DNA damage) in all leukaemia cell lines.

Conclusion: This study is the first to investigate methotrexate and 6-mercaptopurine combined with polyphenols. Data suggest diet-based polyphenols (quercetin, apigenin, emodin, rhein or cis-stilbene) could potentially inhibit the activity of methotrexate and 6-mercaptopurine.

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