

BCL-2 INHIBITION SENSITISES BCL-2-DYSREGULATED / OVEREXPRESSING LYMPHOMA TO THE PRO-APOPTOTIC ACTION OF THE SELECTIVE SEROTONIN REUPTAKE INHIBITOR FLUOXETINE

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BACKGROUND: We previously identified compounds in the SSRI class of antidepressants as being anti-proliferative and pro-apoptotic to the constituent neoplastic cells of Burkitt's lymphoma (BL). Efficacy was deemed achievable within conventional therapeutic doses. A wider range of B-cell malignancy revealed that while broad anti-proliferative action from the SSRI remained, apoptosis was thwarted in the face of Bcl-2-dysregulation / over-expression. Here we have explored the consequence of Bcl-2 inhibition on the pro-apoptotic potential of the SSRI fluoxetine in scenarios where Bcl-2 is dysregulated / over-expressed. **METHODOLOGY:** To illustrate the principle, the following cell lines were selected for study: (i) DoHH2, derived from a case of t(14;18) diffuse large B-cell lymphoma (thereby expressing dysregulated Bcl-2 off the Ig HC/bcl-2 translocation); (ii) KHM2B, derived from a case of BL carrying the hallmark t(8:14) myc/Ig HC translocation plus in addition (and unusually) the bcl-2-dysregulating t(14:18) translocation; (iii) L3055/Bcl-2, BL cells engineered to constitutively over-express a bcl-2 transgene to a (protein) level approximately 5-times that of DoHH2. Apoptosis was followed between 48-96 hours using propidium iodide with an active caspase-3 stain to allow discrimination between viable, early apoptotic, late apoptotic, and necrotic cells. **RESULTS:** In all three cell lines, fluoxetine – while clearly anti-proliferative – failed to deliver apoptosis, either early or late, with full viability maintained throughout culture. Where a Bcl-2 family inhibitor was included, each of the three cell lines now succumbed to fluoxetine's pro-apoptotic drive. Applying optimal synergistic combinations of the two compounds could result in 95% apoptosis of otherwise refractory cells. **CONCLUSION:** A dual therapy modality combining a widely used SSRI with a proven Bcl-2 inhibitor becomes, from the data presented here, a promising option in B-cell tumors otherwise refractory to fluoxetine's pro-apoptotic promise. As fluoxetine accumulates some 20-fold in brain over blood, this option could be particularly attractive in primary CNS lymphoma.