PYRAZOLOTRIAZOLOPYRIMIDINE DERIVATIVES SENSITIZE MELANOMA CELLS TO THE CHEMOTHERAPEUTIC DRUGS: TAXOL AND VINDESINE

1Merighi S, 2Mirandola P, 1Varani K, 1Gessi S, 3Leung E, 4Baraldi PG, 4Tabrizi MA, 1Avitabile A, 1Cattabriga E, 1Iannotta V, 1Pancaldi C, 1Borea PA  
1Dept. of Cl. & Exp. Med., Pharmacology Unit; Univ. of Ferrara, 44100, Ferrara, Italy; 2Dept. of Human Anatomy, Pharmacology and Forensic Medicine, Institute of Normal Human Anatomy, Univ. of Parma, 43100, Parma, Italy; 3King Pharmaceuticals, 27513, Cary, NC, U.S.A.; 4Dept of Pharmaceutical Sciences; Univ. of Ferrara, 44100, Ferrara, Italy

In this study we have evaluated the “in vitro” modulatory activity of a series of pyrazolotriazolopyrimidine derivatives (PTP-d) in sensitizing malignant melanoma cells to the chemotherapeutic drugs: taxol and vindesine. To that end, we have described the impact of chemotherapeutic agents on the cell cycle and on the induction of apoptosis when used alone or in combination with PTP-d. We have demonstrated that four PTP-d reduced chemotherapeutic drugs EC₅₀ doses of the G₂/M accumulation with an average of 1.7 fold for taxol and 9.5 fold for vindesine when challenged on A375 human melanoma cell line. This sensitization activity was also confirmed by analyzing the apoptosis degree induced by the chemotherapeutic drugs. Interestingly, PTP-d had no effects on the response to cytotoxic agents by skin-derived human keratinocyte cells, NCTC 2544. Therefore, we have investigated the signaling pathway sustaining the sensitizing effect of PTP-d, providing functional evidence that active compounds are able to inhibit multidrug resistance-associated ATP-binding cassette drug transporter. These results suggested that PTP-d hold great promise for the treatment of multidrug resistance (MDR) in cancers, leading to potential new therapies for melanoma.

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