Targeting Polo-like kinase 1 provides a new approach to enhance chemosensitivity of rhabdomyosarcoma

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Overexpression of Polo-like kinase 1 (Plk-1) has recently been identified in rhabdomyosarcoma, the most common pediatric sarcoma. Therefore, we investigated the potential of Plk-1 inhibition to sensitize rhabdomyosarcoma cell lines to chemotherapy. Indeed, we show that BI2536, an ATP-competitive small molecule inhibitor of Plk-1, results in cell cycle arrest at G2-phase and subsequently in cell death of rhabdomyosarcoma cells. Furthermore, we found that BI2536 already at low nanomolar concentrations cooperates with Vincristine, a chemotherapeutic that destabilizes microtubules, to induce cell death. Calculation of combination index (CI) revealed that the interaction of BI2536 and Vincristine is synergistic (CI: 0.5). Similarly, BI2536 acts synergistically together with Vinblastine and Vinorelbine, two additional microtubule destabilizing drugs. In contrast, no cooperative interaction was detected for BI2536 together with Taxol, a microtubule stabilizing agent. Mechanistic studies reveal that the combination treatment with BI2536 and Vincristine leads to increased cell cycle arrest in G2 and subsequent activation of caspase-9 and caspase-3. Addition of the pan-caspase inhibitor zVAD-fmk significantly reduces, but does not completely prevent cell death upon treatment with BI2536 and Vincristine. This points to caspase-dependent and -independent mechanisms. As inhibition of Plk-1 does not influence cell viability of non-malignant myoblast cell lines, the synergistic effect of BI2536 combined with conventional chemotherapeutics provides a promising new approach to enhance efficacy of common treatment strategies for rhabdomyosarcoma.