Optimized anti-tumor effects of anthracyclines plus Vinca alkaloids using a novel, mechanism-based application schedule.

Abstract:
Application of anthracyclines and Vinca alkaloids on the same day represents a hallmark of polychemotherapy protocols for hematopoietic malignancies. Here we show, for the first time, that both drugs might act most efficiently if they are applied on different days. Proof-of-concept studies in 18 cell lines revealed that anthracyclines inhibited cell death by Vinca alkaloids in 83% of cell lines. Importantly, in a preclinical mouse model, doxorubicin reduced the anti-tumor effect of vincristine. Both drugs acted in a sequence-dependent manner and the strongest anti-tumor effect was obtained if both drugs were applied on different days. Most notably for clinical relevance, in 34% of 35 fresh primary childhood leukemia cells tested in vitro, doxorubicin reduced the anti-tumor effect of vincristine. As underlying mechanism, doxorubicin activated p53, p53 induced cell-cycle arrest, and cell-cycle arrest disabled inactivation of antiapoptotic Bcl-2 family members by vincristine; therefore, vincristine was unable to activate downstream apoptosis signaling. As molecular proof, antagonism was rescued by knockdown of p53, whereas knockdown of cyclin A inhibited vincristine-induced apoptosis. Our data suggest evaluating anthracyclines and Vinca alkaloids on different days in future trials. Selecting drug combinations based on
mechanistic understanding represents a novel conceptional strategy for potent polychemotherapy protocols.