Abstract

Pediatric Preclinical Testing Program (PPTP) evaluation of rapamycin combined with cytotoxic drugs used frequently in treatment of childhood cancer


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Background: Therapeutic synergy in preclinical models is a promising concept in oncology. The purpose of this study was to determine if antitumor activity of each drug in combination exceeded the antitumor activity of each drug used alone. Therapeutics with therapeutic synergism may allow for reduction in the toxicities of each agent used alone and may provide therapeutic advantage to patients.

Methods: Rapamycin was tested against the PPTP in vitro panel of 23 cell lines at a concentration of 10nM alone or in combination with vincristine, cyclophosphamide, and dexamethasone. Therapeutic synergy was denoted if the LCK value for a combination treatment exceeded the LCK value for a single agent treatment group. The LCK value was computed similarly for the ALL-4 xenograft. Responses to each regimen were compared using the Kaplan-Meier curves for time to event (4-fold increase in tumor volume).

Results: Combining Rap with vincristine was predominantly (-)-additive, while with cyclophosphamide –antitumor activity of Rap combined with either vincristine or cyclophosphamide was enhanced. Rapamycin plus dexamethasone demonstrated a therapeutic advantage over vincristine alone, with complete responses demonstrated in 4 of 4 evaluable animals in the Rap + Dexamethasone group, versus 1 of 4 evaluable animals in the VCR group. The combination of Rap + dexamethasone was tested in three different xenograft models.

Conclusions: Combining Rap with cyclophosphamide in vivo was predominantly -additive or additional effect, except with dexamethasone in the ALL-4 models for which the effect was not additive. In vivo, Rap significantly enhanced the tumor survival times and therapeutic activity of vincristine and cyclophosphamide. Rap combined with vincristine therapy was deemed sufficient to warrant clinical investigation. Rap combined with vincristine demonstrated a superior therapeutic advantage over vincristine alone. Rap combined with dexamethasone was also superior to each agent alone, suggesting a potential therapeutic advantage in the clinical setting. The results of this study indicate that Rapamycin may be a novel drug for the treatment of childhood leukemia.

* Duplication of images is prohibited. A portion of the images is shown below.