

Chemotherapy medication of Vincristine and Vinblastine

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Abstract

Cancers treated with Vincristine and vinblastine include: acute leukemia, Hodgkin's and non- Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumor, multiple myeloma, chronic leukemias, thyroid cancer, brain tumors, non-small cell lung cancer, bladder cancer, melanoma, and testicular cancer andIt is also used to treat some blood disorders. It is given by injection into a vein.

Vincristine and vinblastine exhibit differential activity against tumors and normal tissues. In this work, a number of cultured cell lines were assayed for their sensitivity to the antiproliferative and cytotoxic effects of the two drugs following short-term (4 hr) or during continuous exposures. Differential activity was not seen when cells were subjected to continuous exposures. The concentrations of Vincristine and vinblastine, respectively, that inhibited growth rates by 50% were: mouse leukemia L1210 cells, 4.4 and 4.0 nw; mouse lymphoma S49 cells, 5 and 3.5 nM; mouse neuroblastoma cells, 33 and 15 nw; HeLa cells, 1.4 and 2.6 nw; and human leukemia HL-60 cells, 4.1 and 5.3 nM. In contrast, differential toxicity was seen when cells were subjected to 4-hr exposures and transferred to drug-free medium: the 50% growth-inhibitory concentrations for Vincristine and vinblastine, respectively, for inhibition (a) of proliferation of L1210 cells were 100 and 380 nM and of HL-60 cells were 23 and 900 nM and (b) of colony formation of L1210 cells were 6 and >600 nM and of HeLa cells were 33 and 62 nM. Uptake and release of [3H]- vincristine and [3H]vinblastine were examined in L1210 cells under the conditions of growth experiments. Uptake of both drugs was dependent on the pH of culture media, and significantly greater amounts of [3H]vinblastine than of [3H]vincristine were associated with cells after 4-hr exposures to equal concentrations of either drug. When cells were transferred to drug-free medium after 4-hr exposures, vinblastine was released much more rapidly from cells than was Vincristine, and by 0.5 hr after resuspension of cells, the amount of Vincristine associated with the cells was greater than the amount of vinblastine and remained so for up to at least 6 hr.

Introduction

Vinblastine is a *vinca* alkaloid and a chemical analogue of vincristine. It binds tubulin, thereby inhibiting the assembly of microtubules. Vinblastine treatment causes M phase specific cell cycle arrest by disrupting microtubule assembly and proper formation of the mitotic spindle and the kinetochore, each of which are necessary for the separation of chromosomes during anaphase of mitosis. Toxicities include bone marrow suppression (which is dose-limiting), gastrointestinal toxicity, potent vesicant (blister-forming) activity, and extravasation injury (forms deep ulcers). Vinblastine paracrystals may be composed of tightly-packed unpolymerized tubulin or microtubules.

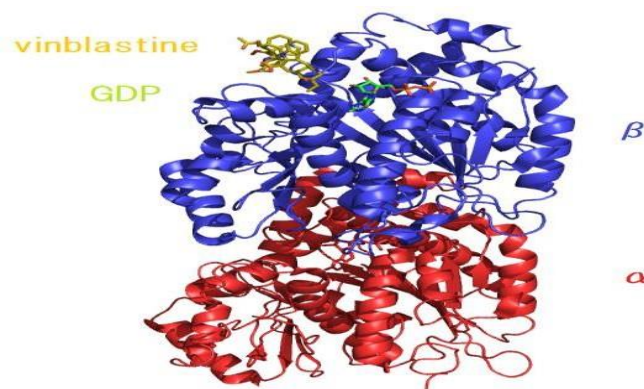
Vinblastine is reported to be an effective component of certain chemotherapy regimens, particularly when used with bleomycin, and methotrexate in VBM chemotherapy for Stage IA or IIA Hodgkin lymphomas. The inclusion of vinblastine allows for lower doses of bleomycin and reduced overall toxicity with larger resting periods between chemotherapy cycles.

Vinblastine is a component of a number of chemotherapy regimens, including ABVD for Hodgkin lymphoma. It is also used to treat histiocytosis according to the established protocols of the Histiocytosis Association.

Vincristine and vinblastine are potent mitotic inhibitors that have been used clinically in the treatment of a variety of neoplasms. The sensitivity of cells to short-term (1- and 4-hr) exposures was also determined for both drugs. Although there were differences in sensitivity to vincristine and vinblastine between cell lines, there was little or no difference in sensitivity to the 2 drugs within a given cell line during continuous exposures.

In contrast, after exposures of 4 hr or less, L1210 and HL-60 cells were much more sensitive to vincristine than to vinblastine. Experiments were undertaken to determine if the difference in sensitivity of L1210 cells to vincristine and vinblastine after short exposures was due to differences in uptake and/or release of the drugs by cells. Others have observed that vinblastine associates with and is released more quickly from rat platelets than vincristine. Radiolabeled vincristine and vinblastine were utilized in assaying uptake and release of drugs from the cells during and following 4-hr exposures. The results obtained suggest that rapid release of vinblastine by cells is the reason for its lesser toxicity, compared with vincristine, after 1- or 4-hr exposures.

Mechanism of Action



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