Antifolate Drugs in Cancer Therapy (Cancer Drug Discovery and Development)

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Antifolates are an important class of anticancer drugs originally developed as anti leu- kemic agents, but now used, usually in combination with other drugs, for the treatment of a wide range of tumors, notably carcinomas of the head and neck, breast, germ cell tumors, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and osteogenic sar- comas. 5-Fluorouracil and its prodrugs also target, in part, the folate-dependent enzyme, thymidylate synthase. Furthermore, folate supplementation in the form of leucovorin, modulates 5-fluororuacil activity. 5-Fluorouracil is widely used in the treatment of colorectal and gastric cancer and in combination for other solid tumors such as breast and head and neck cancers. Ongoing clinical trials with the newer antifolates suggest that the range of solid tumors where these agents will be of use may broaden further. Half a century ago, interesting scientific and clinical discoveries suggested that folie acid was a vitamin involved in vital cellular metabolic processes. The folate analogs, aminopterin and methotrexate, were synthesized by the American Cyanamid Company in an attempt to interfere with these processes and were shown to have anticancer activity by Farber and his colleagues. Hence, the principle of antimetabolite therapy for the treatment of cancer was established. Biomedical research over the following years led to a deeper understanding of the complex biochemical pharmacology of folates and antifolates. Selective antimicrobial agents were discovered, but more tumor-selective anticancer agents did not immediately emerge.

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