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2,4-Diamino-6-(bis-2-chloroethyl)aminomethyl pteridine

A new potent anticancer drug

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Summary. *2,4-Diamino-6-(bis-2-chloroethyl)aminomethyl pteridine has been synthesized and found to be highly potent against L-1210 mouse leukemia lymphoblasts. A single dose of 5 mg/kg injected 24 h after the tumor inoculation increased the life-span of 50% of mice to more than 200%, while the other 50% of animals were cured.*

Introduction

The prevention of DNA synthesis, directly or indirectly, is the main function of many anticancer drugs. Numerous anticancer drugs attack the DNA bases directly, while antifolates such as methotrexate (MTX) act indirectly by inhibiting the activity of dihydrofolate reductase (DHFR). The chemistry and biology of all these compounds are well-documented [1]. Because of their severe side-effects, particularly bone marrow depression, the clinical usefulness of these drugs is somewhat limited.

Recently, a class of compounds with multifunctional groups has been designed by us and predicted to be highly potent [2]. One of these compounds is 2,4-diamino-6-(bis-2-chloroethyl)aminomethyl pteridine, whose structure is shown in Fig. 1.

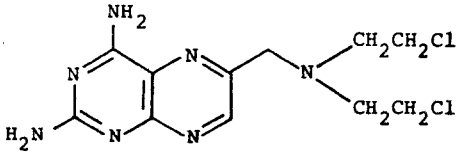

Fig. 1. Chemical structure of 2,4-diamino-6-(bis-2-chloroethyl)aminomethyl pteridine

It can be seen that the compound is composed of the pteroyl part of MTX, covalently linked with the alkylating moiety of an alkylating agent. This communication provides preliminary results showing that the compound is a highly potent anticancer drug.

Materials and methods

2,4-Diamino-6-(bis-2-chloroethyl)-aminomethyl pteridine was synthesized in our laboratory; details of the synthesis will be published elsewhere.

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The anticancer activity of this compound was investigated in B6D2Fl/J female mice, supplied by Jackson Lab., Bar Harbor, Me. During the course of the experiments the animals were maintained in a controlled environment with limited accessibility and were permitted free access to food and water. They were divided into groups of ten animals each. The mice were inoculated IP with 1×10^5 L-1210 mouse leukemia lymphoblasts (originally obtained from Southern Research Institute, Birmingham, Ala) and passaged in DBA/2 mice. Day zero was the day when L-1210 was injected and on the following day, day 1, the treatment was started. Initially the doses of the drug used were 2.5, 5, 10, and 20 mg/kg, given as a suspension in distilled water. For the purpose of studying the apparent toxicity of this drug the above doses were also injected (IP) to normal mice 9–11 weeks of age and weighing 22–25 g. A volume of 0.2–0.3 ml of the suspension was injected into each animal. A single dose was used for both toxicity and activity studies.

Results and discussion

The results of the toxicity studies showed no deaths at the end of 30 days in animals receiving 2.5, 5, 10, or 20 mg/kg. In each of the toxicity studies the animals showed a weight loss of 8% (2.5 mg/kg) to 25% (20 mg/kg) at 5 days after drug injection. However, at 30 days the percentage change in weight was as follows: +15% (2.5 mg/kg); +9% (5 mg/kg); +4% (10 mg/kg); 0% (15 mg/kg); and −7% (20 mg/kg).

The results of the drug activity are summarized in Fig. 2. As can be seen, the drug had a significant effect on the survival of animals following implantation of 1×10^5 L-1210 tumor cells on day 0. Several doses were examined and in each instance there was noticeable prolongation of life-span compared with control animals (broken line in Fig. 2). For example, animals receiving 2.5 mg/kg of the drug had an increased life-span of 190%, while animals receiving 5 mg/kg showed remarkable survival (solid line in Fig. 2). This dose was repeated twice and in each study it showed a similar survival pattern, i.e., 50% of the animals had an increased life-span of more than 200%, while the other 50% of the animals were cured and remained alive even after 90 days. However, those animals receiving the drug at 10 and 20 mg/kg had extended life-spans of 250% and 140%, respectively, and 20% of the animals treated with 10 mg/kg were still alive after 30 days (see Fig. 2). The results obtained with these two doses, 10 and 20 mg/kg, are somewhat puzzling, since the drug did not show any apparent toxicity as mentioned above. Although the explanation for this apparent

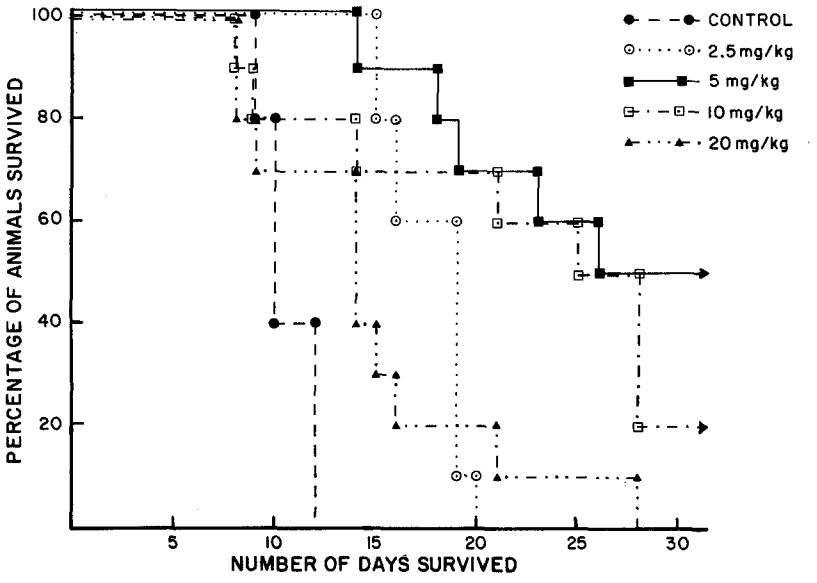

Fig. 2. Survival curve of mice bearing 1×10^5 L-1210 cells. Symbols indicating different doses are given in the figure

discrepancy is presently not known further work is in progress, which may eventually resolve this incompatibility.

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References

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