ONCOLOGY

Antimetastatic Effects of Arbidol, a New Antiviral Drug

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Arbidol, a new antiviral drug, is found to suppress metastases of Lewis' pulmonary carcinoma for various methods of transplantation. The effects of arbidol are compatible with those of the standard interferon inductor poly-I-poly-C.

Key Words: *interferon inductors; arbidol; metastases; Lewis' pulmonary carcinoma*

The use of interferon inductors to treat tumor metastases has been one of the promising trends in the development of new treatment strategies in the last decade. Synthesis of various interferons and some other cytokines induced by them cannot eliminate the primary tumor but does have a marked impact on the level of metastases [6,7]. This lends urgency to the search for new substances characterized by interferon-inducing properties and their trials as antimetastatic agents.

During synthetic investigations in the series of 2-alkyl(aryl)-thiomethyl-5-oxyindole derivatives we found that ethyl ether hydrochloride of 5-hydroxy-4-dimethylaminomethyl-1,2-phenylthiomethyl indole-3-carbonic acid, tentatively named fercaptolin, shows antiviral activity [4].

Further search for new antiviral drugs revealed that one of the fercaptolin analogs, differing from it in the presence of bromine in position 6 (Fig. 1) and called arbidol, is characterized by a high inhibitory effect towards influenza viruses A and B [3]. Moreover, it stimulates interferon production by the organism [2]. After wide-scale clinical trials arbidol was authorized for medical use as an agent for the prevention and treatment of influenza [4].

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The purpose of the present research was to study the antitumor and antimetastatic effects of the new antiviral drug arbidol, possessing interferon-inducing properties, in models of induced and spontaneous metastasizing of Lewis' pulmonary carcinoma.

MATERIALS AND METHODS

Experiments were carried out with male C57Bl/6 mice aged 2 to 3 months. Lewis' pulmonary carcinoma (LPC) was used in the experiments. Intravenous and intramuscular routes of tumor cell

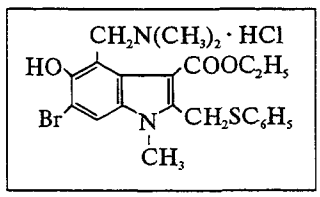

Fig. 1. Chemical formula of arbidol.

transplantation were used to assess the effects of interferon inductors on metastasis. The intramuscular method caused spontaneous metastases from the primary tumor node, while the intravenous method artificially induced metastases. Intramuscular transplantation consisted in injecting into the external part of the left femur 2×10^6 tumor cells in 0.2 ml medium 199 or normal saline. In intravenous transplantation the tumor cells (2×10^5 in

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TABLE 1. Antimetastatic Activity of Poly I:C and Arbidol for Intramuscular Transplantation of LPC Cells (Treatment Started 24 h after Transplantation) ($M \pm m$)

Variant of experiment	Number of metastases in lungs	
	experiment 1	experiment 2
Control (0.2 ml water intraperitoneally or orally)	21.5±1.1 (26)	33.0±2.4 (8)
Poly I:C (50 μg per mouse, intraperitoneally)	13.3±1.8* (8)	15.7±3.6* (7)
Arbidol (orally, 4.1 mg per mouse)	13.5±1.6* (10)	16.0±5.1* (5)

Note. Here and in Tables 2 and 3: number of animals in a group shown in parentheses. Asterisk shows reliable differences ($p<0.05$).

TABLE 2. Antimetastatic Activity of Poly I:C and Arbidol at Intravenous Transplantation of Tumor Cells (Treatment Started 24 h after Transplantation) ($M \pm m$)

Variant of experiment	Number of metastases in lungs	
	experiment 1	experiment 2
Control (0.2 ml water orally or intraperitoneally)	24.4±1.2 (37)	14.0±2.6 (14)
Poly I:C (50 μg per mouse, intraperitoneally)	5.6±1.1* (11)	3.4±2.4* (14)
Arbidol (4.1 mg per mouse, orally)	6.0±1.1* (15)	2.3±1.6* (10)

0.3 ml medium 199 or normal saline) were injected in the caudal vein without heparin, because heparin in such a method of transplantation may noticeably alter the levels of metastasis [5].

The concentration of tumor cells which we used is the maximal permissible, because a higher amount of injected cells causes thromboses and death of the animals. The animals were sacrificed on day 16 after intravenous transplantation of LPC cells and on day 22 after intramuscular transplantation. Prepared animal lungs were put for 24 h into Bouin's fluid, and the number of metastases on the lung surface was counted through a magnifying glass at ×8.

The standard interferon inductor poly I:C was used for a comparative assessment of the antimetastatic properties of arbidol. Poly I:C (polyribosyl inosinic, polyribosyl cytidinic acid, Calbiochem) was administered parenterally in a dose of 50 μg per mouse weighing 20 g in 0.2 ml normal saline once in 6 days. Arbidol, an antiviral agent with interferon-inducing properties, was administered orally in 1% starch solution in a dose of 4.1 mg per mouse weighing 20 g in accordance with the recommended therapeutic dose exerting an inhibitory effect on influenza viruses.

RESULTS

In our experiments with induced and spontaneous metastasis of LPC we attempted to assess the capacity of arbidol for suppressing metastases and to compare it to that of the standard agent poly I:C. The results of these experiments for the intramuscular and intravenous routes of tumor cell administration, respectively, are summed up in Tables 1 and 2. It is evident, that arbidol is not inferior to poly I:C in its efficacy of suppressing LPC metastases to the lungs, but differs from it favorably in degree of toxicity. Hence, it was interesting to examine the relationship between the efficacy of metastases suppression and the period elapsing between tumor graft and the beginning of therapy. The data on how the starting time of treatment affected the suppression of metastases with arbidol are presented in Table 3. As with

TABLE 3. Effect of the Time of Arbidol Administration on LPC Metastases for Intravenous and Intramuscular Tumor Cell Transplantation ($M \pm m$)

Arbidol, variant of experiment	Level of metastasis, % of control	
	i.v. graft	i.m. graft
24 h before graft, 4.1 mg per mouse orally, once in 6 days	25.0±11.3* (19)	39.5±21.4* (20)
24 h after graft, as above	25.5±11.1* (15)	33.5±21.6* (10)
5 days after graft, as above	40.0±22.4* (16)	70.2±22.9 (19)
8 days after graft, as above	75.0±22.0 (15)	80.3±20.0 (10)

poly I:C, the therapeutic effect of arbidol in respect of metastases suppression was lower if therapy was started later, this pointing to the inability of interferon inductors to eliminate already existing micrometastases, which commonly develop 7 days after tumor cell transplantation.

It is noteworthy that we used therapeutic doses of the drug in our experiments, which are one order of magnitude lower than the maximal tolerable doses. Other effects of arbidol on the immune system, besides its ability to induce interferon, have not been described. The antimetastatic effect of arbidol described here once more indicates that substances characterized by interferon-inducing activity potentially exert an antimetastatic effect as well. However, some molecular biological features of the effect of arbidol on cells, associated with inhibition of transmembrane nucleotide transport, have been described [1], so that the possibility of this agent's directly influencing proliferating tumor cells, reducing the level of metastasis, cannot be ruled out.

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