The Value of Levamisole in a Wilms' Tumor Animal Model

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Key Words

Levamisole
Wilms' tumor
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Abstract

The effect of Levamisole was studied in an animal model of Wilms' tumor. No tumoricidal effect of Levamisole could be documented in this tumor model, and no effect was shown on prevention of tumor, when Levamisole was given before tumor implantation. In previous experience with Wilms' tumor model, a good correlation between the human and animal tumor was found in regard to treatment with different drugs. The fact that Levamisole had no effect on our animal model and its reported immunosuppressive effect at some doses, should be considered in planning clinical trials.

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Introduction

In 1971, Renoux [1] described the effect of antihelmintic Levamisole¹ on potentiation of the bacterial vaccine in mice. Since then the immunological properties of this compound were extensively studied [2].

It has been suggested that Levamisole restores the depressed cellmediated immunity [3], and some apparently successful clinical trials have been reported [4].

On the other hand, an enhancement of tumor growth was noted [5], and most recently Peters et al. [6] have observed that the dose of Levamisole may be of critical importance in clinical trials, since in different doses it may either suppress or enhance tumor growth.

Table I. Results with Levamisole treated animals with Wilms' tumor.

No. of
Levamisole
Tumor
Days of
Metastatic
animals
dose
wt. (g)
survival
index
19

1 mg/kg
 87.81 ± 14.72
 33
 ± 2
 12%
 19
 2 mg/kg
 148.8
 ± 14.5
 38 ± 1
 33%
 17
 4 mg/kg
 170.6 ± 24.6
 37 ± 2
 29%
 20
 8 mg/kg
 129.3 ± 13.7
 37 ± 1
 5%
 35
 control
 148.1 ± 11.9
 37 ± 1
 25%

1 p < 0.005 as compared to control

2 ± = One standard error

In this report an animal model of Wilms' tumor [7] was chosen to study the effects of Levamisole in broad dose range on this tumor model which was selected as a suitable basis for experimentation because it closely follows the clinical condition in man [7–9].

Materials and Methods

Young adult male Wistar/Furth rats purchased from Microbiological Associates (Walkersville, Maryland) were maintained in the Department of Experimental Surgery at Roswell Park Memorial Institute on stock pellets (Teklad)² and water ad libitum. The Wilms' tumor was donated by Dr. P. TOMASHEFSKY in 1973. It currently is in its 50th transfer generation in Wistar/ Furth Strain.

All surgical procedures were performed under light anesthesia and aseptic technique was observed. Wilms' tumor was removed from donor animals. It was minced and prepared so that a piece of solid tumor, 1—2 mm, was injected by means of a trocar in the axillary region of the tested animal. 167 rats were implanted with Wilms' tumor. 53 animals served as controls and received no further therapy. The remaining 114 tumor-bearing rats were divided into different groups. One group of 19 animals received Levamisole 1 mg/kg at the day of tumor implantation. The three other groups of 19, 17 and 20 rats respectively, received Levamisole 2, 4 and 8 mg/kg on the implant day.

An additional group of 20 animals received Levamisole 4 mg/kg one day prior to tumor implant, and another group of 19 animals began Levamisole treatment 4 mg/kg one day following the implant. All rats, except controls received Levamisole every day until the death of the animal. The weight of the animals and of the tumors were recorded, and necropsy was performed on all animals.

Results

The control group had a mean tumor weight of 148.1 g and survived 37 days (table I). 25% of the animals in this control group were noted to have distant metastases. No statistically

1 Levamisole hydrochloride powder (R12564), lot No. SM 18,538.R. & D. Janssen Inc., New Brunswick, New Jersey.

2 ARS/Sprague Dawley, Division of Mogul Corp., Winfield, Iowa.

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Table 11. Results with Levamisole 4 mg/kg/day treated animals with Wilm's tumor.

Levamisole has shown no effect and this should be considered in planning clinical trials, while keeping in mind the reported immunosuppressive effect of Levamisole at some doses. More studies on the effect of Levamisole in different tumor models with wide dose ranges are indicated before more clinical applications are considered.

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significant differences were found between all groups as compared to the controls, in regard to survival, and/or in regard to the occurrence of metastases. There was no difference between groups in regard to the dosage of Levamisole used or whether it was injected before or after tumor implantation. Only the animals which received 1 mg/kg of Levamisole daily showed significant tumor weight reduction (mean tumor weight 87.8 g, as compared to controls, mean tumor weight 148.1 g, $p < 0.005$) although no difference was found in the survival or metastatic rate.

Pretreatment by Levamisole (table II) did not result in any significant tumor weight reduction or survival prolongation, and it did not diminish the metastatic rate.

Discussion

Levamisole in our study did not display the tumoricidal effect previously demonstrated with cytotoxic therapy in this tumor model [9]. No effect was shown on prevention of the tumor, when Levamisole was given before or on the day of tumor implantation. This is in contrast to the report of Ibrahim et al. on antitumor effects of Levamisole in hamster melanoma and rat hepatoma [10].

Most recently, Peters et al. [6] observed no anticarcinogenic or tumoricidal effect on 7,12-dimethylbenz (a) anthracene (DMBA) induced mammary cancer treated by Levamisole. This is similar to our experience, although we did not observe an enhancement of tumor growth as was reported by Peters, when 8 mg/kg Levamisole was given [6].

It seems that animal tumor models are responding variably to Levamisole in wide dosage ranges, although no such dose related effect was noted in our study.

In our previous experience with Wilms' tumor model, a good correlation between the human and animal tumor was found in regard to treatment with different drugs [9]. In our model,

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