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Effects of Gallium and Lanthanum on Experimental Tumor Growth

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Abstract—*The effects of gallium and lanthanum compounds on DS sarcoma growth were studied. Under the stated experimental conditions gallium showed no tumor inhibition while lanthanum did. The probable mechanisms of action which explain this behavior are discussed on the basis of their pharmacological properties (calcergens) and of the influence of treatment procedure.*

INTRODUCTION

GALLIUM nitrate inhibition of rodents tumor growth in various transplanted tumors has been already reported [1]. Initial clinical studies indicate a minor evidence of antineoplastic effect on several types of human tumors [2].

From the pharmacological point of view lanthanum is an element which shows similar effects to that of gallium as a direct calcifier (calcergen) [3]. La^{3+} and Ga^{3+} show dramatic effects on Ca^{2+} metabolism. La^{3+} is a competitor for Ca^{2+} sites [4, 5], an inhibitor at Ca^{2+} sites [6] and a blocking agent of the Ca^{2+} transport mechanism [7–10]. La^{3+} has been shown to provoke profound alterations in calcium metabolism of tumor cells [11]. It is able to form more stable complexes with nucleic acids, nucleoproteins and phospholipids than Ca^{2+} [12–15] and in this way to impair most of the cell physiological and genetic functions.

In the present experimental work we have compared the tumor inhibition effect of Ga^{3+} and La^{3+} on an experimental sarcoma.

MATERIALS AND METHODS

Male Wistar rats (body weight 210–220 g) were injected s.c. in the inguinal region with 2×10^7 viable DS sarcoma tumor cells suspended in 0.2 ml of saline. Twenty-four hours after inoculation the animals were divided randomly into five groups. Groups a and b received 2.5 mg of gallium element i.p. as nitrate or as aspartate in 0.25 ml of saline respectively while groups c and d were injected with 2.5 mg of lanthanum element as chloride or aspartate respectively. The administration i.p. of gallium or lanthanum was repeated daily for 6 days. A control group received no treatment.

All animals were sacrificed 12 days after tumor cells inoculation and the tumors were excised and weighed. Body and tumor weights of the different groups are shown in Table 1. To determine the level of significance the experimental results were subjected to statistical analysis using Wilcoxon's rank test.

RESULTS

The statistical analysis indicates that both gallium compounds show a significant difference between the means of tumor weight increase taken on treated groups and control group ($P<0.1$ and $P<0.01$ for gallium nitrate and gallium aspartate respectively). On the contrary, a significant weight decrease ($P<0.1$) was observed in the lanthanum chloride treated group. Lanthanum aspartate showed no statistically significant difference.

DISCUSSION

Tumor growth inhibition can be accomplished by interference with biochemical processes of the tumor cell (cytotoxicity), by impairment of the genetic apparatus (DNA-intercalation), or by increasing the immunodefence capabilities of the host.

DS sarcoma is a chemically-induced tumor

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Table 1. Effects of gallium and lanthanum treatment on DS sarcoma growth

Group	No. of tumors	Tumor weight (g)		Body weight (g)	Intraperitoneal calcification
Control	17	4.82±1.14		243.9±2.9	–
Gallium nitrate	18	8.62±1.63	($P<0.1$)	211.9±6.4	+
Gallium aspartate	22	10.9±2.00	($P<0.01$)	217.5±5.1	–
Lanthanum chloride	18	3.72±0.96	($P<0.1$)	220.0±4.4	+ + +
Lanthanum aspartate	16	5.76±1.59	(ns)	230.3±4.2	+ +

All values are means±S.D.

[16] which presents tumor-specific antigens developing an antitumor immunoreaction in the host which under the experimental conditions of our protocol determines 20–30% of tumor rejection after s.c. inoculation. These characteristics and its resistence to some chemotherapeutics [16] make this tumor model more suitable for tumor growth inhibition evaluation than other transplantable animal tumors more sensitive to chemotherapeutics or which are taken up without eliciting the host immunological reaction. Nevertheless, experimental data already published on lymphatic leukemia BW5147 and lymphosarcoma 6C3HED [17], animal tumors without antigenic properties, are in perfect agreement with the present findings. Under the same experimental conditions (treatment beginning 24 hr after inoculation, i.p. injection of the antitumor agent), a slight increase of tumor growth was observed for gallium-treated animals while the opposite effect was showed by lanthanum-treated animals.

These experimental results indicate that under the stated experimental conditions gallium compounds show no value as tumor inhibiting agents. On the other hand, lanthanum compounds present a minor but statistically significant inhibition handicapped by an important systemic toxicity. The principal manifestations of toxicity for both gallium and lanthanum compounds arç renal lesions which are similar to those associated with the administration of *cis*-diamminedichloroplatinum [18]. These lesions seem to be provoked by occluding tubular precipitates of calcium phosphate complexed with gallium or lanthanum, behavior which is in agreement which their calcergenic properties [19].

It is probable that the effects of these elements on tumor growth are related to their systemic effects instead of a local accumulation. At least in the case of gallium, it seems that there is no selective retention of the element by the tumor when compared to most normal tissues [20].

The use of this type of antitumor agents which show the advantage of having no significant myelosuppressive toxicity emphasizes on the interest to know the possible mechanism or mechanisms involved in their action. La^{3+} and Ga^{3+} provoke changes in Ca^{2+} metabolism of tumors [11, 21]. The patterns of these modifications are different. Ionic replacement determined by ion size and valence of each ion is involved in this reaction. The ionic radii of La^{3+}, Ga^{3+}, Ca^{2+} and Mg^{2+} are 1.15, 0.62, 0.99 and 0.65 Å respectively. These values indicate that according to the ionic model for chemical bonding [22, 23] La^{3+} will replace Ca^{2+}, and GA^{3+} will replace Mg^{2+}. This does not exclude that under certain conditions of steric fitting replacement of Ca^{2+} by Ga^{3+}, and Mg^{2+} by La^{3+} can take place. Now, if we consider the unique role played by Ca^{2+} in cell membranes transport, mitochondrial physiology and cell division, the effects of La^{3+} on cell structure and functions must be of great importance. Nevertheless, Mg^{2+} is an important ion in cytoplasmic membrane function as well as in a great number of enzymatic systems. Changes of its intracellular concentration show considerable effects on cell division and growth [24]. The possible importance of calcium metabolism impairment in tumor inhibition is pointed out by the experimental facts that compounds with antitumor activity such as vincristine, daunomycin, adriamycin and ruthenium red show effects on Ca^{2+} transport and binding by the cell [25–28].

The quantitative differences observed in local calcification of the host by La^{3+} and Ga^{3+} reflect the differences of the reactions involved. Bearing in mind these differences the effects of both ions on tumor cells can be interpreted as follows: La^{3+} induces a tumor growth inhibition by impairment of

membrane transport [29] and of the mitochondrial bioenergetic system. On the contrary, Ga^{3+}, by competition binding to Mg^{2+} sites, induces a change of cell membrane permeability [30] leading to an influx of Ca^{2+}, and to an increase of free intracellular Mg^{2+}; two conditions which can act positively on cell proliferation [31]. Therefore, the effects of Ga^{3+} are the combination of two processes, one is the calcergenic action similar to that of La^{3+} and the other a free Mg^{2+} releasing replacement of ions. How the balance of these effects will lean on one or other direction is probably a matter of Ga^{3+} administration procedure. For this reason, the present results on Ga^{3+} inhibition of tumor growth do not exclude the possibility that under other experimental conditions (e.g., intravenous perfusion) a tumor growth reduction due to a La^{3+}-like action can overwhelm the Mg^{2+} releasing effect.

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