

Antitumor activity of polyacrylates of noble metals in experiment

Larisa A. Ostrovskaya ^{1,*}, David B. Korman ¹, Natalia V. Bluhterova ¹, Margarita M. Fomina ¹,
Valentina A. Rikova ¹, Claudia A. Abzaeva ², Larisa V. Zhilitskaya ², Nina O. Yarosh ²

¹N.M. Emanuel Institute of Biochemical Physics Russian Academy of Sciences, 4 Kosigin St., 119991, Moscow, Russia

²A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky St., 664033, Irkutsk, Russia

*Corresponding author email address: larros@list.ru

ABSTRACT

The aim of this research has been the study of the antitumor activity of polymetalacrylate derivatives containing in their structure noble metals. Metallic derivatives of polyacrylic acid were not previously tested as antitumor agents. The antitumor activity of polyacrylates, containing argentum (argacryl), aurum (auracryl) and platinum (platacryl) against experimental models of murine solid tumors (Lewis lung carcinoma and Acatol adenocarcinoma) as well as acute toxicity have been studied. It is found that the polyacrylates of noble metals are able to inhibit tumor growth up to 50-90% in comparison with the control. Auracryl induced the inhibition of the Lewis lung carcinoma and Acatol adenocarcinoma by 80 and 90% in comparison with the control, results recommending it for further advanced preclinical studies.

Keywords: Polyacrylates of noble metals, experimental antitumor chemotherapy, transplantable tumors of animals.

1. INTRODUCTION

Despite the certain progress achieved in recent years in antitumor chemotherapy, the search of new classes of antitumor agents is still an actual problem and therefore, it constitutes one of the most essential part of investigations in the field of biomedical chemistry and experimental oncology.

The discovery of novel chemical structures with original mechanisms of action could extend the effectiveness of chemotherapy, as original and acquired drug resistance of tumors is emerging [1].

In this connection, the metal derivatives of polyacrylic acid, i.e. polymetalacrylates (PMA), related to the new for oncology group of compounds non-studied earlier in such aspect, are rather promising.

The pharmacological mechanism of action of bioactive PMAs is based on their influence on blood coagulating, particularly, on the ability to form copolymers with blood plasma proteins. One of PMA named as "Ferracryl" is approved for medical usage in Russia as an anti-bleeding agent [2, 3].

Such mechanism of action makes it possible to consider the compounds above as potential antitumor drugs, capable to inhibit tumor growth, impacting to their blood supply.

Besides that it is also well known that compounds containing in their structure complexes of metals such as for example platinum derivatives (cisplatin, carboplatin *et al.*) are among the most effective drugs in the modern antitumor chemotherapy [1].

The acute toxicity and antitumor activity of more than twenty PMA derivatives containing various metals have been previously reported. It was found that all the investigated compounds manifest an antitumor activity in more or less degree, but the most effective were agents that contained noble metals, such as silver, gold, platinum [2-8].

This paper deals with the data on acute toxicity evaluation and antitumor activity study of polyacrylates of noble metals on experimental models of transplanted murine solid tumors.

2. EXPERIMENTAL SECTION

2.1. Compounds

Three metal derivatives of polyacrylic acid, containing argentum (argacryl), aurum (auracryl) and platinum (platacryl) have been studied in this experiment. The PMA investigated compounds represent incomplete metallic salts of polyacrylic acid containing noble metal ions (4-8 mass %) and correspond to the general formula $(-\text{CH}_2-\text{CH}-\text{COOH})_n(-\text{CH}_2-\text{CH}-\text{COOM})_m$, where $n = 1200-3500$; $m = 1650-6650$. The molecular weight of these PMA are in the range of 1000000 to 3000000 D. Absorption bands were $1548-1540 \text{ cm}^{-1}$ ($\nu_{\text{as}} \text{ COO}^-$) и $1405-1410 \text{ cm}^{-1}$ ($\nu_{\text{s}} \text{ COO}^-$); $1694-1649 \text{ cm}^{-1}$ (COOH), with a widened band in the region $3420-2554 \text{ cm}^{-1}$, shifted in a low-frequency field (associated OH).

The preparations are colorless or colored films. All tested compounds have a good solubility in water.

Argacryl, auracryl and platacryl were used as aqueous solutions injected, intraperitoneally (i/p) for five times in daily doses close to 1/10 from their maximum tolerated doses (MTD), starting from the next day after tumor transplantation, as follows: argacryl - 2 mg/kg, auracryl - 20 mg/kg, platacryl - 4 and 10 mg/kg.

2.2. Laboratory Animals

Experiments have been carried out on 150 inbred BDF₁ and Balb/c males mice, with the body weight of 18-20g (Nursery "Stolbovaya" of the Russian Academy of Medical Sciences).

The animals feeding regimen was based on the usage of the standard certificated commercial dry extruded food for rodents

(PK-120-1) [9]. Preclinical studies involving laboratory animals respected all special rules that included demands and recommendations for humanitarian and ethical aspects of such kinds of experiments [9].

2.3. Experimental Models

Solid tumors of mice, such as Lewis lung carcinoma and Acatol adenocarcinoma, transplanted subcutaneously to the animals according to the standard procedures have been used as experimental test-systems [9].

2.4. The Antitumor Activity Test

Kinetics of the tumor growth in groups of treated (T) and control (C) animals as well as duration of mice life-span in both groups have been studied. The coefficient of the tumor growth inhibition (TGI, %) and the increasing of the mean life-span ($\Delta\tau$, %) of mice has been determined according to the equation: $TGI = (P_C - P_T)/P_C \%$; $\Delta\tau = (\tau_C - \tau_T)/\tau_C \%$, where P_C and P_T are volumes (or weights) of tumor, and τ_C and τ_T are the mean life-span of the control group and group of treated animals, respectively. Minimal significant parameters have been considered to be $TGI > 50\%$ and $\Delta\tau > 25\%$ [9]. Two mutually perpendicular sizes of the tumor node have been measured over the whole period of tumors development for the study of the kinetics of the tumor

growth. The tumor volume has been measured according to the formula for an ellipsoid as $V = ab^2/2$, where a is the length, b is the width and height of a tumor node. The tumor weight corresponded to its volume, since the density of a tumor tissue was generally agreed to be equal to 1 g/cm^3 [9]. The groups of treated and control animals comprised six and eight mice, respectively. Each experiment was repeated two or three times. Experimental animals were observed during the whole period of the development of tumors. The results of the main experiments are represented as kinetic curves of the tumor growth in groups of treated and control animals. Each dot on these curves presents the mean value of the tumor weight for 12-18 mice. Computer program "Statistics 6.0" was used for the statistical analysis of experimental data. F-criterion significance test was used for the estimation of the confidence interval of differences between mean values of tumor weight in groups of treated and control animals. It was considered that difference between values of tumor weight in groups of treated and control animals was significant if the estimated value "F" was higher than the value of "F-criterion" known for prescribed level of significance and for the certain degrees of freedom (f_1 ; f_2) [9].

3. RESULTS SECTION

The acute toxicity and antitumor activity of polyacrylates of noble metals on experimental models of transplanted murine solid tumors have been studied.

3.1. Acute Toxicity

Parameters of acute toxicity of polyacrylates of noble metals on intact BDF₁ mice - the mean lethal doses (LD_{50}) and the maximum tolerated doses (MTD) are shown in Table 1. It was found that the toxicity of the studied agents depended on the nature of the metal involved into polymer. From the data indicated in the Table 1 it results that auracryl has a lower toxicity than the other studied polymetalacrylates, the LD_{50} and the MTD for auracryl being 100 and 150 mg/kg respectively. The same parameters for platacrly are equal to 50 and 75 mg/kg, but for argacryl - 25 and 20 mg/kg, respectively (table 1).

3.2. Antitumor Activity

The study of antitumor activity of argacryl, auracryl and platacrly has been conducted in optimum schedule of drugs application i/p, every day, five times starting from the next day after tumor transplantation in daily doses equal to 2, 20 and 10-4 mg/kg, respectively.

The influence of auracryl and argacryl on the kinetics of growth of murine solid tumors - Lewis lung carcinoma and Acatol adenocarcinoma is shown in Figures 1 and 2, respectively.

The sensitivity of tumors to tested PMA compounds are characterized by data represented in Table 2.

As it could be seen from data presented below argacryl has exhibited ab extremely strong antitumor effect against Lewis lung carcinoma - the tumor growth inhibition being equal to 90% and the life-span of treated animals increased with 46% in comparison with control (Fig.1A; Table 2).

Acatol adenocarcinoma had also some sensitivity to the argacryl action. This agent inhibited the growth of Acatol

adenocarcinoma with 55% in comparison with control (Fig.1B; Table 2).

Auracryl, as it is evidence from the presented data, is strongly effective against both tumor strains. Tumor growth inhibitory effect of this drug against Lewis lung carcinoma and Acatol adenocarcinoma was by 80% and 90% in comparison with control (Fig.2A, B; Table 2).

It should be noted that auracryl treatment induced an almost complete inhibition of tumor growth for a very long period of time. Thus, the growth of Acatol adenocarcinoma was with on 90% in comparison with control during 17 days after termination of drug administration or during 22 days after tumor transplantation (Fig.2B; Table 2).

Auracryl also increased the antitumor effect of hyperthermia. The single intravenous injection of auracryl one hour before hyperthermia session increased the effectiveness of such kind of therapy with 30 to 70% against Lewis lung carcinoma as well as against Acatol adenocarcinoma [6]. Antitumor activity of platacrly was less intensive than that of auracryl and argacryl. Its effectiveness against Lewis lung carcinoma and Acatol adenocarcinoma has not been exceeding 45% and 60% of tumor growth inhibition in comparison with control (Table 2).

Thus, the results of this study are evidencing the pronounced and significant antitumor effect of auracryl and argacryl against some murine solid tumors, such as Lewis lung carcinoma and Acatol adenocarcinoma.

The inhibition of Lewis lung carcinoma and Acatol adenocarcinoma, as affected PMA, is observed to be between 55-90% in comparison with control. Their activities depend on compound structures, doses and tumor types (Table 2).

Thereby, the obtained experimental data give evidence that auracryl is inhibiting the growth of Lewis lung carcinoma and

Acatol adenocarcinoma on 80 and 90% in comparison with control respectively, being the most effective drug among studied PMAs, this agent being recommended for further advanced preclinical studies. Results presented in this work are in good connection with the well known data about antitumor activity of organic compounds contained in their structure some metals especially platinum and ferrocene. Currently, studies of the antitumor activities of organometallic compounds, in particular, metallocenes, are vigorously carried out all over the world including Russia, Japan, Republic of South Africa, USA, European countries, Pakistan, Brazil. A broad range of metallocene derivatives and p-cyclopentadienyl-p-arene

transitionmetal (Ti, Zr, Hf, V, Mo, Fe, Co, Ru) complexes have been investigated; functional derivatives of ferrocene are studied extensively. The search for active compounds among various metal complexes was also stimulated by the appearance of the first effective metal-containing cytostatic agent, cis-diamminodichloroplatinum [10]. In particular antitumor activity of some ferrocene derivatives such as ferrocenylalkyl azoles, ferrocenylalkyl nucleobases and especially ferrocene-modified thiopyrimidines was shown recently [11-14]. It may be assumed that revealed in this study new data about antitumor activity of polyacrylates of noble metals will promote the new investigations of metal-organic compounds as potential antitumor drugs.

Table 1. The acute toxicity of polymetalacrylates of noble metals

Drugs*	The maximum tolerated dose (MTD) mg/kg	The mean lethal dose (LD ₅₀) mg/kg
Argacryl (Ag)	20	25
Auracryl (Au)	100	150
Platacryl (Pt)	50	75

* The single i/p administration of drugs to intact BDF₁ mice.

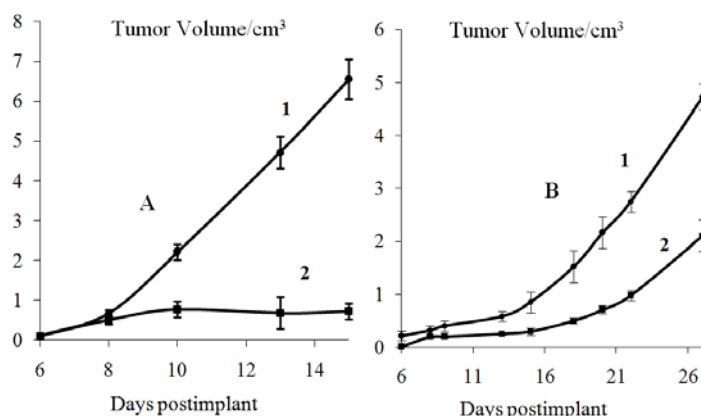


Figure 1. Antitumor activity of argacryl against Lewis lung carcinoma (A) and Acatol adenocarcinoma (B); 1 - control; 2 - argacryl 2 mg/kg, daily, i/p, 1-5 days postimplant.

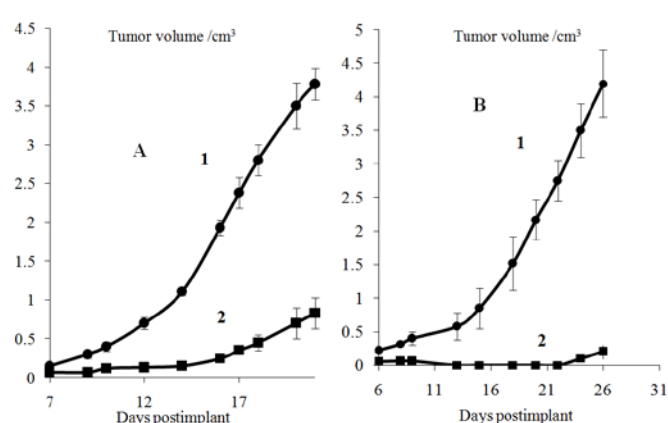


Figure 2. Antitumor activity of auracryl against Lewis lung carcinoma (A) and Acatol adenocarcinoma (B); 1 - control; 2 - auracryl 2 mg/kg, daily, i/p, 1-5 days postimplant.

Table 2. Antitumor activity of polyacrylates of noble metals against murine solid tumors

Tumor model	Daily dose (mg/kg)*	Day postimplant	The mean tumor weight (g)		The coefficient of tumor growth inhibition TGI (%)	F _{0.001} -criterion significance test (f ₁ = 15; f ₂ = 11)
			Treated animals	Control animals		
ARGACRYL						
Lewis lung carcinoma	2	15	0.7±0.1	6.5±0.4	90**	7.10 > 4.25
Acatol adeno-carcinoma	2	27	2.1±0.2	4.7±0.6	55	5.06 > 4.25
AURACRYL						
Lewis lung carcinoma	20	21	0.8±0.1	3.8±0.5	80	5.44 > 4.25
Acatol adeno-carcinoma	20	27	0.5±0.1	4.7±0.6	90	9.00 > 4.25
PLATACRYL						
Lewis lung carcinoma	10	21	2.1±0.1	3.8±0.5	45	5.44 > 4.25
Acatol adeno-carcinoma	4	21	2.1±0.3	5.0±0.6	60	5.06 > 4.25

* Intraperitoneal injection, five times, 1-5 days postimplant

** Increasing of the mean life-span of treated animals on 46% in comparison with control
The mean life-span of treated and control animals is 34.5± 4.6 and 25.0 ± 2.8 days, respectively

4. CONCLUSIONS

The antitumor activity of polyacrylates of noble metals, containing argentum (argacryl), aurum (auracryl) and platinum (platacryl) has been studied against experimental models of murine solid tumors (Lewis lung carcinoma and Acatol adenocarcinoma). It has been found that the polyacrylates of noble metals are prospective to inhibit tumor growth on 55-90% in

comparison with control. Auracryl is the most effective drug among the studied PMAs, inhibiting the growth of Lewis lung carcinoma and Acatol adenocarcinoma with 80 and 90% in comparison with the control. Auracryl can be recommended for further advanced preclinical studies of its antitumor activity and mechanisms of action.

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