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Biodistribution Studies of a New Antitumor Compound Based on Nanoporous Nanodiamond Composite Labeled with Rhenium-188

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Abstract

This study evaluated a new drug delivery system for local radiotherapy on the base of nanoporous nanodiamond composites (NDC) labeled with β-emitting radionuclide rhenium-188. The biodistribution of labeled compound was assessed after intratumoral (i.t.) and intramuscular (i.m.) injection. 24 mice-bearing solid Ehrlich carcinoma xenografts received i.t. injections of 0.370 ± 0.074 MBq ^{188}Re-nanoporous diamond composites. Another 24 intact mice were injected with the same preparation intramuscularly. The samples of different organs and tissues were collected for gamma count.

After i.t. and i.m. administration of ^{188}Re-nanoporous NDC a considerable amount of radioactivity retained at the site of injection. In tumor tissue the total amount of activity decreased from 92.68 % to 9.63 % of injected dose (ID) throughout the study. The removal of injected activity from muscular tissue was faster as compared with tumor tissue, and declined from 81.06 % to 8.40 % ID for up to 72 h. Therefore, after i.m. injection the accumulation of radioactivity in healthy organs and tissues was slightly higher than after i.t. injection. In conclusion, it was demonstrated that ^{188}Re-nanoporous diamond composites had the potential radiotherapeutic significance.

Keywords: composite materials, nanodiamond, rhenium-188, cancer radiotherapy, local radiotherapy.

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1. Introduction

Carbon-based nanomaterials such as carbon nanotubes, fullerenes, nanodiamonds, graphene and its derivatives have attracted considerable attention in recent years in nanomedicine due to their unique properties and biocompatibility [1-3]. It is possible to synthesize composite materials with defined mechanical properties and use them to create vector containers for targeted delivery of drugs and/or radionuclides.

Nanodiamond composites (NDC) consists of nanodiamond particles with a mean size of 4–6 nm and a nanosize graphite-like matrix coating the surfaces of the nanodiamond particles and bonding them into a composite [4]. They possess a high biocompatibilty with human cells and a high porosity, which may be used for takeover, storage and long-term emission of drugs and/or radionuclides by creating durable containers. For example, these containers with synthetic antibacterial drug levofloxacinum suppressed the development of inflammatory processes in osteal tuberculosis in chinchilla rabbits as compared with control group [4]. In addition, NDC allow compensating bone defect, arising from the inflammatory process in the bone [4]. There was also shown the possibility of the composites to target drug delivery to central nervous system [5].

^{188}Re (17 h half-life, $E_{\beta max}$ = 2.12 MeV (84%)) is of current interest for the variety of therapeutic applications. It also has a gamma-line at 155 keV (16%) allowing imaging at a gamma-camera. The beta emissions of ^{188}Re have a sufficient penetration over a maximum range of 10.8 mm for the tumor ablation, involving pericapsular lesions and avoiding damage to adjacent nontumorous tissue. Also the cross-fire effect is possible, a consequence that avoids the need to target every cell within the tumor and to internalize the radionuclide in each targeted cell. Due to these advantages, ^{188}Re offers the possibility of higher energy deposition in a shorter time period relative to radionuclides with longer half-lives.

In this aspect, containers based on nanoporous NDC can serve as a convenient biocompatible vehicle for radionuclide delivery. The aim of this study is to investigate the biodistribution of nanoporous NDC labeled with ^{188}Re after single intratumoral or intramuscular injection in mice.

2. Materials and methods

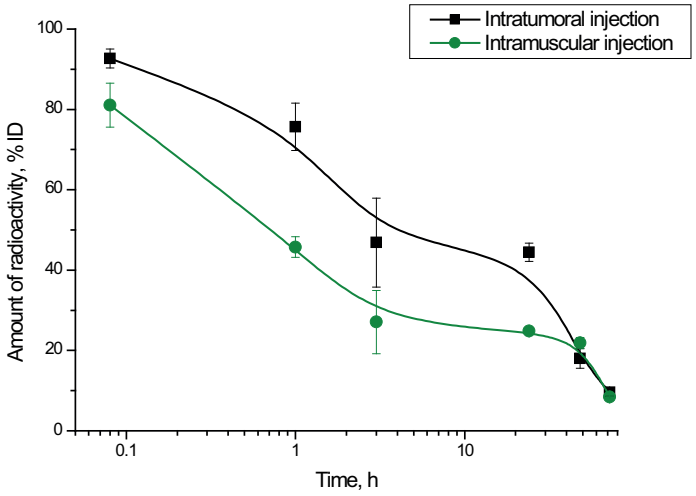
Biodistribution study of nanoporous NDC labeled with ^{188}Re was carried out in male mice aged 8–9 weeks and about 20 g in weight. 48 mice were divided into 2 equal groups (24 animals in each group). Mice in group 1 received intratumoral (i.t.) injection of ^{188}Re-nanoporous diamond composites. For obtaining the solid Ehrlich carcinoma mice with ascites were used. Tumor cells ($3.5.10^6$ in 0.1 ml) were implanted subcutaneously into the right hip of each mouse. I.t. injection was performed in a week, when the tumor volume reached 0.4-0.6 ml. Animals in group 2 received intramuscular (i.m.) injections of ^{188}Re-nanoporous NDC. Injected activity was 0.370 ± 0.074 MBq (10 ± 2 mCi) in a volume 0.1 ml.

The animals were sacrificed by decapitation at 5 min, 1, 3, 24, 48 and 72 h after injection. Four mice were taken for each time point. Dissection began by drawing blood from the aorta. Then the organs were dissected, washed, dried placed in plastic tubes and weighed. The radioactivity was measured by automated gamma-counter «Wizard» (version 2480 «PerkinElmer/Wallac», Finland). The amounts of radioactivity were calculated as percent of injected dose per gram of tissue (% ID/g). Also an activity at the place of injection (tumor or muscle) as percent of injected dose was calculated.

The results from the biodistribution data for each group of mice were expressed as mean value and standard error of the mean ($M \pm m$). Student's t test was used to analyze data throughout all studies between groups at different time points, and $p<0.05$ was considered statistically significant.

3. Results and discussion

The studies revealed a remarkable retention of radioactivity at the site of injection, i.e. in tumor tissue and femoral muscle of mice. After i.t. injection of ^{188}Re-nanoporous NDC the total amount of activity decreased from 92.68 % to 9.63 % ID for up to 72 h. The absorption of the radioactivity after i.m. injection is faster than after i.t. injection probably due to high vascularity of the muscle tissue. After i.m. administration the level of radioactivity at the site of injection declined from 81.06 % to 8.40 % ID as time increased (Figure 1). Previously we have shown high tumor retention (at least 45.9 % ID) of larger ^{188}Re-nanoporous NDC in tumor-bearing rats [6].



intratumoral or intramuscular administration of ^{188}Re-nanoporous diamond composites in mice (in % of injected dose).

Figure 1: The excretion of radioactivity after

In blood the highest levels of specific radioactivity were 1.70 % ID/g (at 5 min) and 1.89 % ID/g (at 1 h) after i.t. and i.m. administration, respectively. It is noteworthy that the amount of activity after i.m. injection was slightly higher as compared to that after i.t. injection, except the first term after injection.

In thyroid high uptakes of activity were observed after introducing of ^{188}Re-nanoporous NDC by various routes of administration. After i.t. injection initial amount of activity was 7.44 – 7.61 % ID/g, then it went up to 17.01 % ID/g (at 3 h) and dropped rapidly within 24-72 hours. After i.m. injection the level of radioactivity reached 23.68 % ID/g, but then declined slower as compared with i.t. administration.

A significant amount of radioactivity was also determined in stomach after i.m. injection (Table 1). The maximum uptake (11.60 % ID/g) occurred at 3 h post-injection, but then decreased rapidly. In lungs the peak activity was 1.59 % ID/g and occurred immediately after i.t. injection. After i.m. injection activity increased from 0.39 % ID/g to 1.29 % and 1.21 % ID/g at 1 h and 3 h, respectively.

The uptakes in other soft organs and tissues were less than 1 % ID/g after i.t. and i.m. routes of administration. It should be emphasized that in tumor-bearing mice the highest uptakes were observed in 5 min after i.t. injection and then declined throughout the study. In contrast, after i.m. injection the levels of radioactivity in soft organs rose up to maximal values within 1-3 h, but then decreased.

4. Conclusion

In summary, the biodistribution data showed the retention of significant part of injected radioactivity mainly at the place of injection after direct intratumoral and intramuscular administration of ^{188}Re-nanoporous NDC.

However, there are some differences in ^{188}Re-nanoporous NDC biodistribution after various routes of administration. The higher amount of activity retained in tumor tissue than in muscle. Therefore after i.m. injection soft organs and tissues uptake of activity was more intensive, especially within 3 h after injection. The results demonstrated that ^{188}Re-nanoporous NDC had the potential for clinical applications in radiotherapy and can be further evaluated for establishing as a radiopharmaceutical for human use.

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Table 1: Biodistribution of radioactivity after intratumoral injection of ^{188}Re-nanoporous diamond composites in mice with solid Ehrlich carcinoma and after intramuscular injection in healthy mice (in % of injected dose per gram).

	Organ/tissue	Time after injection					
		5 min	1 h	3 h	24 h	48 h	72 h
1	Blood	1.70±0.05* 0.47±0.06** p<0.001	0.38±0.11 1.89±0.09 p<0.001	0.16±0.02 1.63±0.18 p<0.001	0.14±0.03 0.23±0.03 p>0.05	0.03±0.01 0.10±0.03 p>0.05	0.05±0.01 0.05±0.01 p>0.5
2	Thyroid	7.61±1.52 1.61±0.49 p<0.02	7.44±0.72 19.90±2.21 p<0.002	17.01±3.43 23.68±2.56 p>0.1	1.90±0.17 9.01±2.53 p<0.05	0.11±0.03 2.39±0.29 p<0.001	0.81±0.12 0.33±0.06 p<0.02
3	Lungs	1.59±0.28 0.39±0.07 p<0.01	0.12±0.01 1.29±0.13 p<0.001	0.12±0.01 1.21±0.07 p<0.001	0.16±0.02 0.13±0.02 p>0.25	0.013±0.004 0.039±0.006 p<0.02	0.006±0.001 0.032±0.009 p<0.05
4	Liver	0.73±0.05 0.19±0.04 p<0.001	0.10±0.02 0.91±0.05 p<0.001	0.064±0.003 0.832±0.042 p<0.001	0.096±0.017 0.111±0.018 p>0.5	0.026±0.005 0.029±0.007 p>0.5	0.054±0.008 0.025±0.006 p<0.05
5	Kidneys	0.70±0.05 0.22±0.03 p<0.001	0.14±0.03 0.95±0.07 p<0.001	0.09±0.01 0.91±0.03 p<0.001	0.08±0.01 0.10±0.03 p>0.5	0.11±0.01 0.05±0.02 p<0.05	0.09±0.03 0.06±0.01 p>0.25
6	Heart	0.39±0.03 0.22±0.02 p<0.01	0.37±0.02 0.25±0.03 p<0.02	0.39±0.06 0.48±0.07 p>0.25	0.07±0.01 0.07±0.02 p>0.5	0.08±0.01 0.07±0.02 p>0.5	0.05±0.02 0.04±0.01 p>0.5
7	Spleen	0.58±0.06 0.11±0.02 p<0.001	0.06±0.03 0.74±0.05 p<0.001	0.051±0.005 0.794±0.051 p<0.001	0.060±0.004 0.069±0.008 p>0.25	0.020±0.007 0.102±0.028 p<0.05	0.048±0.005 0.074±0.013 p>0.1
8	Stomach	1.08±0.17 0.22±0.06 p<0.01	0.87±0.05 7.53±0.85 p<0.001	1.02±0.10 11.60±2.19 p<0.01	0.98±0.14 1.59±0.14 p<0.05	0.019±0.003 0.497±0.111 p<0.01	0.015±0.003 0.085±0.015 p<0.01
9	Muscle	0.25±0.01 0.09±0.01 p<0.001	0.09±0.01 0.45±0.11 p<0.02	0.04±0.01 0.24±0.03 p<0.001	0.04±0.01 0.07±0.04 p>0.25	0.016±0.004 0.084±0.022 p<0.05	0.035±0.008 0.090±0.020 p<0.05
10	Femur	0.410±0.050 0.024±0.003 p<0.001	0.04±0.01 0.05±0.01 p>0.5	0.04±0.01 0.10±0.02 p<0.05	0.06±0.01 0.06±0.02 p>0.5	0.16±0.06 0.05±0.02 p>0.1	0.08±0.02 0.05±0.01 p>0.1
11	Place of injection	118.32±10.40 106.47±18.57 p>0.5	89.73±11.49 61.42±3.56 p>0.05	111.97±9.90 43.46±12.84 p<0.01	71.25±17.57 37.31±4.01 p>0.1	20.35±2.75 37.30±5.69 p<0.05	11.45±2.25 15.95±1.75 p>0.1

* – intratumoral administration

** – intramuscular administration

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