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ORIGINAL

Behavioral studies of mice with breast cancer after treatment with new anticancer agent, Rh2-containing arginine-graphene

Estudios de comportamiento de ratones con cáncer de mama después del tratamiento con un nuevo agente anticancerígeno, arginina-grafeno que contiene Rh2

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Abstract

Objectives: Ginsenoside Rh2-containing arginine-reduced graphene (Gr-Arg-Rh2) is a new designed anticancer nondrug for treatment of cancer. In this study, behavior of mice with breast cancer was evaluated after treatment with Gr-Arg-Rh2.
Methods: Thirty-two cancerous mice were divided into 4 groups and treated every three days for a duration of 32 days: Group 1, PBS: 60 µl (6 mg/kg), Group 2, Rh2: 60 µl (6 mg/kg), Group 3, Gr-Arg: 70 µl (3 mg/kg), and Group 4, Gr-Arg-Rh2: 70 µl (3 mg/kg). Behavioral demonstrations were assessed following the treatment.
Results: Results showed that the mice treated with the Gr-Arg and Gr-Arg-Rh2 appeared to be more energetic than Rh2 and control groups.
Conclusions: Based on the results, Gr-Arg-Rh2 can reduce cancer-related fatigue and low energy in cancerous patients.

Key words: Ginsenoside Rh2-containing arginine- highly porous graphene, Ginsenoside Rh2, Breast Cancer, Energy, Fatigue.

Resumen

Objetivos: El grafeno reducido con arginina que contiene ginsenósido Rh2 (Gr-Arg-Rh2) es un nuevo fármaco anticanceroso diseñado para el tratamiento del cáncer. En este estudio, se evaluó el comportamiento de ratones con cáncer de mama tras el tratamiento con Gr-Arg-Rh2.
Métodos: Treinta y dos ratones con cáncer fueron divididos en 4 grupos y tratados cada tres días durante 32 días: Grupo 1, PBS: 60 µl (6 mg/kg), Grupo 2, Rh2: 60 µl (6 mg/kg), Grupo 3, Gr-Arg: 70 µl (3 mg/kg), y Grupo 4, Gr-Arg-Rh2: 70 µl (3 mg/kg). Se evaluaron las manifestaciones conductuales tras el tratamiento.
Resultados: Los resultados mostraron que los ratones tratados con el Gr-Arg y el Gr-Arg-Rh2 parecían tener más energía que los grupos Rh2 y control.
Conclusiones: Según los resultados, el Gr-Arg-Rh2 puede reducir la fatiga y la baja energía relacionadas con el cáncer en los pacientes cancerosos.

Palabras clave: Grafeno altamente poroso con arginina, Ginsenósido Rh2, Cáncer de mama, Energía, Fatiga.

Introduction

Cancer-related fatigue and low energy are very common in various cancers[1]. Approximately 80-100% of cancerous patients have these complications[2]. This type of fatigue is different from the fatigue of daily life[3]. Most cancer patients complain of weakness, lethargy, fatigue and low energy[4]. Fatigue in movement, eating, walking, showering, etc. are common in these patients[5]. Patients with breast cancer are no exception. The fifth leading cause of cancer-related death in women is breast cancer[6]. Various strategies can be used for reduction of cancer-related fatigue and low energy such as exercise, yoga, massage therapy, counseling, nutritional counseling[7,8]. Plant-derived compounds can have multiple biological effects[9]. Ginseng and active ingredients derived from it, is one of these plants with effective biological substances[10]. In our previous study, we showed that Ginsenoside Rh2-containing arginine-reduced graphene, nanostructures with the most important agent derived from Ginseng, have potent anticancer activity against various cancers[11]. On the other hand, it's proven that both American and Asian ginseng, is a promising treatment for fatigue[12]. Given that these researchers, in this article, we evaluated the effect of Gr-Arg-Rh2 on reduction of cancer-related fatigue and low energy in mice with breast cancer.

Methods

Thirty three mice with breast cancer were included in this study. All experimental protocols were approved by the Ethical Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (Project code: IR.SSU.fm.REC.1397.42). The conditions of keeping the mice were suitable, and they were provided with the right food and water. These mice were divided to four groups:

Group 1) PBS as placebo controls (N=8), group 2) Rh2 (N=8), group 3) Gr-Arg (arginine-treated highly porous graphene) (N=8), and group 4) Gr-Arg-Rh2 (Rh2 -treated Gr-Arg) (N=8). The mice were given intravenous injections of the drug or a placebo every three days and 10 times during 32 days. Mobility and vibrancy are considered as factors associated with life quality in cancerous patients. We evaluated the distances traveled and velocities of the animals' movements as a mobility and vibrancy assessment method. For this evaluation, the entire animal mobility was recorded by a video camera 24 hours a day. The dimensions of all cages were the same. We also evaluated the animal's ability to hang from its tail. For each group, the mean of tail hangings for all the mice was evaluated. The mean distance traveled by the mice along the area of the cage was also calculated for each group. These two acquired sets of data were comprised among the examined groups.

Results

During the treatment period, the mice treated by Gr-Arg-Rh2, indicated a significant increase in the distance moved and velocity compared with other groups. In those mice treated by Gr-Arg-Rh2, the mean of tail hanging rates was significantly higher than other examined groups. This group was more likely to escape when hung from the tail. They seemed to have more energy and looked healthier. In addition, the mice treated by the Gr-Arg appeared to be more energetic than Rh2 and control groups.

Discussion

The distance traveled and velocity of the animals' movements were considered as an assessment of mobility and vibrancy. In breast cancer treatment, different disorders such as fatigue, mood swings, anxiety, as well as cognitive impairments were reported in most of the survivors. These disorders lead to an impairment in the quality of life during and after chemotherapy. Similar behaviors were seen in the animal model, especially in rodent models. Santos et al. revealed that tumors or tumor resection can affected the behavior of the mice in a nyctohemeral (day/night)-dependent manner[13]. Chemotherapy can also change the patients' behavior by directly affecting their brain with oxidative stress, inflammation, and neurovascular damage. This disorder is called chemotherapy-induced behavioral deficit[14]. Loman et al. showed that increased fatigue and decreased cognitive performance in paclitaxel-treated mice were related to an increase of circulating chemokine and pro-inflammatory cytokine/chemokine in the brain[15]. As mentioned above, in our study, the mice in Gr-Arg-Rh2 and Gr-Arg groups had more energy and were healthier than other groups. The improvement of the healing process and the reduction of cancer-induced- inflammation can be the main reason behind the increased levels of energy and mobility in the mice of these two groups.

Conclusion

Results showed that Gr-Arg-Rh2 can reduce cancer-related fatigue and low energy in cancerous patients.

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Competing interests

The authors declare no competing interests.

References

1. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. The oncologist. 2007;12(S1):4-10.

2. Stone PC, Minton O. Cancer-related fatigue. European journal of cancer. 2008;44(8):1097-104.

3. Silva FD. Myriad of Cancer-related Fatigue: A Concept Model on Multifactorial Causation and Impact. Indian Journal of Palliative Care. 2021;27(2):354.

4. Iop A, Manfredi A, Bonura S. Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. Annals of oncology. 2004;15(5):712-20.

5. Farajollahi M, Alikhani M, Farmani F, Hosseini F. Fatigue in cancer patients receiving chemotherapy. Iran Journal of Nursing. 2004;16(36):47-52.

6. Nash Z, Menon U. Ovarian cancer screening: Current status and future directions. Best practice & research Clinical obstetrics & gynaecology. 2020;65:32-45.

7. Schmidt ME, Milzer M, Weiß C, Reinke P, Grapp M, Steindorf K. Cancer-related fatigue: Benefits of information booklets to improve patients' knowledge and empowerment. Supportive Care in Cancer. 2022:1-9.

8. Agbejule OA, Hart NH, Ekberg S, Crichton M, Chan RJ. Self-management support for cancer-related fatigue: A systematic review. International Journal of Nursing Studies. 2022:104206.

9. Saklani A, Kutty SK. Plant-derived compounds in clinical trials. Drug discovery today. 2008;13(3-4):161-71.

10. Shin B-K, Kwon SW, Park JH. Chemical diversity of ginseng saponins from Panax ginseng. Journal of ginseng research. 2015;39(4):287-98.

11. Zare-Zardini H, Taheri-Kafrani A, Amiri A, Bordbar A-K. New generation of drug delivery systems based on ginsenoside Rh2-, Lysine- and Arginine-treated highly porous graphene for improving anticancer activity. Scientific Reports. 2018;8(1):586.

12. Arring NM, Millstine D, Marks LA, Nail LM. Ginseng as a treatment for fatigue: a systematic review. The Journal of Alternative and Complementary Medicine. 2018;24(7):624-33.

13. Santos JC, Bever SR, Pereira-da-Silva G, Pyter LM. Tumor resection ameliorates tumor-induced suppression of neuroinflammatory and behavioral responses to an immune challenge in a cancer survivor model. Scientific Reports. 2019;9(1):752.

14. Vichaya EG, Chiu GS, Krukowski K, Lacourt TE, Kavelaars A, Dantzer R, et al. Mechanisms of chemotherapy-induced behavioral toxicities. Front Neurosci. 2015;9:131-.

15. Loman BR, Jordan KR, Haynes B, Bailey MT, Pyter LM. Chemotherapy-induced neuroinflammation is associated with disrupted colonic and bacterial homeostasis in female mice. Scientific Reports. 2019;9(1):16490.