

The Benefits of Magnetic/Protein Targeted Drug Delivery in Treating Skin Cancer in-Vivo

Heath E. Misak*, Farhana Abedin, Michelle Man, Jennifer Herring
Faculty: Ramazan Asmatulu, Shang-You Yang[#]

Department of Mechanical Engineering, College of Engineering

[#] Department of Biological Sciences

Abstract. Skin cancer represents the most common type of cancers, and is life threatening without treatment. People with light skin, genetic diseases and high exposure to ultraviolet radiation (UVR) are at a high risk of developing skin cancer. Skin cancer once developed may spread to the rest of the body including organs inside the body. Once the cancer advances and metastasizes, it is difficult to control and treat. We report on a magnetic carrier system (MCS) that is capable of localizing the chemotherapy at the afflicted area. In-vivo experiments have shown that utilizing the MCS developed at Wichita State University (WSU) the efficacy of the chemotherapy can be enhanced at least twofold.

Introduction

Cancer is a disease in which malignant cells grow in an uncontrolled fashion, intrude into nearby tissue, damage healthy tissue and spread to remote organs/tissues. It is estimated that in 2010; 569,490 deaths occurred in the United States due to cancer, and of that 11,790 deaths are expected to occur because of skin cancer [1]. Although skin cancer is not the most deadly form of cancer, it is the most common form of cancer in the United States. More than 3.5 million cases are diagnosed a year (2006)[2], and 1 out of 5 Americans will develop skin cancer in the course of a lifetime [3].

Skin Cancer can be classified as melanoma or nonmelanoma. The two main types of nonmelanoma skin cancer are Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC). BCC skin cancer is by far the most common form of skin cancer with 2.8 million cases diagnosed each year in the United States (2005)[3]. BCC skin cancer can be disfiguring if the tumor is allowed to grow, however this form of cancer is not fatal. SCC skin cancer can spread to other parts of the body, including the lining of the hollow organs of the body, passages of the respiratory and the digestive tracts. SCC skin cancer is reported in 700,000 people a year in the United States.

There are many forms of treatments for skin cancer, and treatment of basal cell carcinoma has a good chance of success of 90% or more [4]. However, other forms of skin cancer such as SCC do not see as high of success rates.

Excision surgery is the typical method of treating skin cancer; however excision surgery is not always applicable because of medical condition of the

patient, location of cancer (eyes, inner organs), recurring skin cancer and large areas affected by skin cancer. Chemotherapy can be used when surgery is not feasible or as an adjuvant regime, however novel ways must be developed to reduce toxicity and increase efficacy. One such way is to use magnetic targeted drug delivery system (DDS), and we evaluate this novel DDS in treatment of SCC skin cancer in mice.

Method

A DDS was produced by oil in oil emulsion process [5, 6]. The DDS consisted of 500 nm nanospheres with 5 constituents: 34.5% poly(lactic-co-glycolic acid) (PLGA), 34.5% Albumin, 20% Fluorouracil (5-Fu), 10% magnetic nanoparticles and 1% 1,6-Diphenyl-1,3,5-hexatriene (DPH). The emulsion process was dispersed at a rate of 10,000 rpms for 1.5 hours. The DDS was centrifuged to remove the oil, washed 6 times with hexane to remove any remaining oil residue. The DDS was then vacuum filtered with 200 nm filter paper. The DDS was allowed to sit in a vacuum for three days to remove any excess solvent. All the surgical procedures on mice have been approved by the Institutional Animal Care and Use Committee. 20 mice were injected with SCC cells on the left and right hip, and the tumors were allowed to grow until the tumor was distinguishable from the injection. The mice were split into 4 groups of 5 mice (n=5). The 1st group was the control, and no treatment was given. The 2nd group was locally injected with the DDS around the tumor into the subcutaneous, and the 3rd was also injected in the same manner; but a magnet was glued to the tumor after each injection for an hour. The 4th group was injected in the same manner as group 2 and 3; however, as received 5-Fu was injected instead of the DDS. The mice were injected four times every 2 days, except one injection that was done 3 days after the previous injection.

The tumors were assumed to be in the shape of a rectangle. Thus, the area of the tumor was characterized by measuring the longest width of the tumor and the perpendicular direction from the measured length in the middle of tumor. The two measurements were taken every Monday, Tuesday and Friday for 19 days after the first injection.

Results and Discussion

Comparing the right tumor to the left tumor, it was seen that all 4 treatments to the left side tumor had little effect on the right side tumor. The left side tumor control group displays an exponential growth with a high exponent compared to the other groups, thus the three other treatments are successful in reducing the growth of the tumor. From fig. 1 and fig. 2, it can be seen that the treatment of the DDS has reduced the growth of the tumor compared to the control. The tumor growth of the DDS + magnet has further reduced the growth. This suggests that magnetic targeting DDS has improved the efficacy of the treatment by preventing diffusion of the DDS throughout the body. The pure 5-Fu injections have shown a similar response to growth rates as the DDS + magnet, however after 9 days from the injections the tumor growth displayed a more exponential growth reflecting that of the control. This suggests the DDS + Magnet is successful in releasing the 5-Fu for a longer time, and has the benefit of a lower dosage. Thus, utilizing magnetic target drug delivery the efficacy of IP injections for skin cancer can be improved.

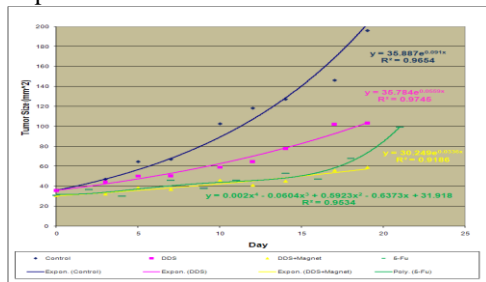


Fig. 2. The tumor size vs. time showing the growth of the four groups: Control, DDS, DDS + Magnet and 5-Fu.

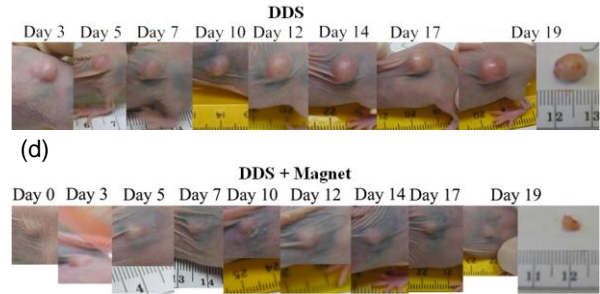
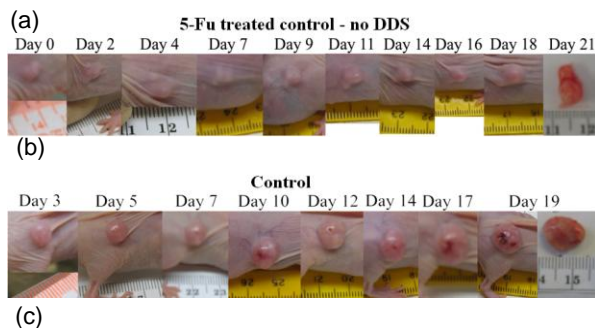


Fig. 3. A visual comparison of the SCC tumors growth with respect to time showing the four groups: 5-Fu (a), control (b), DDS (c) and DDS + Magnet (d).

Conclusions

We found that tumors were significantly shrunk after treating the mice with the chemo-drug containing DDS. In addition, the therapeutic effect significantly increased when external magnetic field was applied. The DDS exhibited longer tumor inhibition effect than drug-infusion alone. The magnetic targeting DDS may improve the efficacy of the treatment by preventing the DDS dissemination. Data indicates using this in-vivo system that magnetic target drug delivery can be beneficial in use in applications where the chemotherapy must be held in one location, controlled release of the chemotherapy is desirable and a small carrier system is advantageous. Further investigation is warranted to explore the dose titer and long-term safety issues.

Acknowledgment

We would like to thank Via Christi Health and The Orthopedic Research Institute (ORI) for the funding of this project.

- [1] American Cancer Society. "Cancer Facts & Figures 2010," Atlanta: American Cancer society; 2010.
- [2] H. W. Rogers, *et al.*, "Incidence estimate of nonmelanoma skin cancer in the United States, 2006," *Arch Dermatol*, vol. 146, pp. 283-7, Mar 2010.
- [3] J. K. Robinson, "Sun exposure, sun protection, and vitamin D," *JAMA*, vol. 294, pp. 1541-3, Sep 28 2005.
- [4] (1996-2010, 8/5). *Skin Cancer (Nonmelanoma Skin Cancer)*. Available: http://www.medicinenet.com/skin_cancer/article.htm
- [5] H. Misak, *et al.*, "The Efficacy of Magnetic Target Drug Delivery to Treat Skin Cancer," in *Society For Biomaterials*, Orlando, FL, 2011.
- [6] R. Asmatulu, *et al.*, "A Magnetic Targeted Drug Delivery System for Rheumatoid Arthritis," in *SAMPE Fall Technical Conference*, Salt Lake City, UT, 2010, p. 10.