ORIGINAL ARTICLE

Evaluation of a combination tumor treatment using thermo-triggered liposomal drug delivery and carbon ion irradiation

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The combination of radiotherapy with chemotherapy is one of the most promising strategies for cancer treatment. Here, a novel combination strategy utilizing carbon ion irradiation as a high–linear energy transfer (LET) radiotherapy and a thermo-triggered nanodevice is proposed, and drug accumulation in the tumor and treatment effects are evaluated using magnetic resonance imaging relaxometry and immunohistology (Ki-67, n = 15). The thermo-triggered liposomal anticancer nanodevice was administered into colon-26 tumor-grafted mice, and drug accumulation and efficacy was compared for 6 groups (n = 32) that received or did not receive the radiotherapy and thermo trigger. In vivo quantitative R_1 maps visually demonstrated that the multimodal thermosensitive polymer-modified liposomes (MTPLs) can accumulate in the tumor tissue regardless of whether the region was irradiated by carbon ions or not. The tumor volume after combination treatment with carbon ion irradiation and MTPLs with thermo-triggering was significantly smaller than all the control groups at 8 days after treatment. The proposed strategy of combining high-LET irradiation and the nanodevice provides an effective approach for minimally invasive cancer treatment. (Translational Research 2017;■:1–10)

Abbreviations: LET = linear energy transfer; DDS = drug delivery system; MTPL = multimodal thermosensitive polymer-modified liposome; MR = magnetic resonance; MRI = magnetic resonance imaging; IMRT = intensity-modulated radiation therapy; DNA = deoxyribonucleic acid; PEG = polyethylene glycol; $MnSO_4$ = manganese sulfate; EYPC = egg-yolk phosphatidylcholine; DOPE = dioleoylphosphatidylethanolamine; ODVE = octadecyl vinyl ether; EOEOVE = 2-(2-ethoxy)ethoxyethyl vinyl ether; SOBP = spread-out Bragg peak; HIMAC = heavy ion medical accelerator in Chiba; TR = repetition time; TE = echo time; FOV = field of view; NEX = number of averages; T_1 = longitudinal relaxation time; RARE = rapid acquisition with relaxation enhancement; RAREVTR = variable repetition and echo time RARE sequence; ANOVA = analysis of variance; R_1 = longitudinal relaxation rate; Gy = gray; RBE = relative biological effectiveness; DOX = doxorubicin; RNA = ribonucleic acid

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Submitted for publication March 19, 2016; revision submitted April 12, 2017; accepted for publication April 13, 2017.

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1931-5244

http://dx.doi.org/10.1016/j.trsl.2017.04.001

AT A GLANCE COMMENTARY

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Background

The combination of radiotherapy with chemotherapy is one of the most promising strategies for cancer treatment. Here, a novel combination strategy utilizing carbon ion irradiation as a high–linear energy transfer (LET) radiotherapy and a thermo-triggered nanodevice is proposed, and drug accumulation in the tumor and treatment effects are evaluated using magnetic resonance imaging (MRI) relaxometry and immunohistology (Ki-67, n = 15).

Translational Significance

In vivo quantitative R_1-maps visually demonstrated that the multimodal thermosensitive polymer-modified liposomes (MTPLs) can accumulate in the tumor tissue regardless of whether the region was irradiated by carbon ions or not. The tumor volume after combination treatment with carbon ion irradiation and MTPLs with thermo-triggering was significantly smaller than all the control groups at 8 days after treatment. The proposed strategy combining high-LET irradiation and the nanodevice provides an effective approach for minimally invasive cancer treatment.

INTRODUCTION

The combination of radiotherapy and chemotherapy, known as chemoradiotherapy, is one of the most common strategies for cancer treatment.[1] Recent technological advances in both radiotherapy and chemotherapy have the potential to further improve tumor treatment. For example, intensity-modulated radiation therapy has been developed for better control of radiation doses in accordance with tumor shape and position.[2,3] Intensity-modulated radiation therapy has been applied to optimize cancer treatments in lung,[4,5] breast,[6-8] and prostate.[9,10] As another example, high–linear energy transfer (LET) particle therapy using protons and heavy ions, in particular carbon ions, has been developed for more precise and confined irradiation.[11] A heavy-ion beam directly causes DNA double-strand break so that apoptotic and necrotic death of tumor cells is induced.[12] Thus, heavy-ion beams have the potential to improve the treatment for hypoxic and/or radiation-resistant tumors. At our institute (National Institute of Radiological Sciences, NIRS), clinical treatment using a carbon-ion beam began in 1994 and by 2014 over 8000 patients have been treated.[11,13] Advances in beam-line technology have allowed tumors in tissues such as lung,[14] head and neck,[15,16] and prostate[17] to be targeted with carbon ions. The combination therapies with carbon-ion irradiation and chemotherapy also were performed.[13,18] However, carbon-ion radiotherapy cannot be applied to the metastatic phase of cancer growth because the total required irradiation dose exceeds safety limits. Thus, for carbon-ion radiotherapy to be most effective it is necessary to combine it with additional treatment strategies.

With regards to advances in chemotherapy, several nanoparticle-based drug carriers, such as micelles, liposomes, and dendrimers, have been developed to increase the efficiency of drug accumulation in tumor and to minimize side-effects.[19,20] Several nanoparticles that have prolonged half-life in the bloodstream show higher passive accumulation in tumor tissues, which is a phenomenon known as the enhanced permeability and retention effect.[21] PEGylated liposomal doxorubicin (DOXIL/Caelyx, Janssen Pharmaceutical, Inc., Titusville, N.J.) has been used clinically to treat ovarian cancer and Kaposi sarcoma. Micelles that incorporate cisplatin (NC6004, Nanocarrier, Japan),[22,23] paclitaxel (NK105, Nihon-Kayaku, Japan),[24,25] and epirubicin (NC6300, Nanocarrier, Kowa, Japan)[26,27] have also been evaluated in clinical trials. However, accumulation of these nanoparticles in the tumor region cannot be monitored and evaluated in vivo. Recently, a number of research groups have developed theranostic nanoparticles that contain both therapeutic drugs for treatment and contrast agents that aid visualization of drug distribution with an in vivo imaging modality or a window chamber system.[28-32] In previous work, we investigated the multimodal thermosensitive polymer-modified liposomes (MTPLs) containing $MnSO_4$ as an magnetic resonance (MR) contrast agent, rhodamine as a fluorescence dye, and doxorubicin (DOX) as an anticancer drug and as a possible theranostic tool.[30] It was found that the transformation of the thermosensitive polymer when heated to over 41°C allows the contents of the MTPLs to be released. MTPL accumulation in the tumor region can also be visualized with MRI and fluorescence imaging, and treatment effects after heating increased significantly.

Previously, conventional radiotherapy combined with a PEGylated nano-drug delivery system (DDS) was reported to enhance treatment efficacy as increases in tumor size were controlled and survival duration was prolonged.[33-36] Although in vitro studies for the proton beam radiotherapy combined with temperature-sensitive liposomes has been reported,[37,38] there is no in vivo report of a high-LET beam radiotherapy, such as a charged proton or carbon beam, combined with nano-DDS therapy. There is also no report of a combined therapy using