Contrast enhanced MRI guided photodynamic therapy for non-invasive treatment of cancer

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Introduction:

Photodynamic therapy is a minimally invasive, specific cancer treatment procedure, involving activation of a photosensitizer in the tumor tissue with light irradiation. The challenge for effective cancer treatment with photodynamic therapy is visualization of the accurate location of the tumor target for specific light activation. MRI is a non-invasive modality and can provide detailed three-dimensional anatomical information with high spatial resolution. Contrast enhanced MRI with macromolecular MRI contrast agents can accurately detect and locate solid tumors and has a potential to guide site-specific irradiation to non-invasively treat solid tumors with photodynamic therapy. We have explored contrast enhanced MRI guided photodynamic therapy to non-invasively treat solid tumor in an animal tumor model with a paramagnetically labeled polymeric drug delivery system of a photosensitizer mesochlorin e_6. A Gd-DOTA labeled poly-(L-glutamic acid)-mesochlorin e_6 (Mce_6) conjugate was prepared to deliver the photosensitizer. The efficacy of MRI-guide photodynamic therapy was evaluated in an animal model bearing MDA MB-231 breast carcinoma xenografts. Gd-DOTA labeled poly-(L-glutamic acid) was used as a control. Contrast enhanced MRI clearly revealed the drug accumulation in the solid tumor and the location of the tumor. Light irradiation of the solid tumor resulted in significant tumor regression as compared to the control.

Experimental methods:

Poly-(L-glutamic acid) (PGA) conjugate containing Mce_6, and DOTA-Gd (*Pol*$_1$) was synthesized. DOTA-Gd was attached to PLGA via 1,6-hexanediamine and the drug was directly conjugated to the polymer. PGA-(Gd-DOTA) conjugate without the drug (*Pol*$_2$) was also synthesized as a control. Molecular weights of the conjugates were determined using SEC. Gd (III) and Mce_6 contents were determined using ICP-OES and UV spectrophotometry, respectively. T_1 relaxivity of the conjugates was determined using standard inversion recovery sequence on a Siemens Trio 3T Scanner. Two groups of female nu/nu athymic mice bearing MB231 breast carcinoma xenografts were intravenously injected with the conjugates at a dose corresponding to 0.07 mmol-Gd/kg for *Pol*$_2$ and 0.07 mmol Gd/kg and 6 mg-Mce_6/kg for *Pol*$_1$. The animals were scanned on a Siemens Trio 3T MRI scanner before and at 5, 15, 30 minutes, 1, 2 and 18 hours post injection using a 3D FLASH pulse sequence with fat suppression. The animals were treated at 18 and 24 hours post injection with a laser of wavelength 650 nm for 15 minutes at a dose of 200 J/cm^2. Efficacy of photodynamic therapy was evaluated by assessment of tumor volume and survival rates over 90 days in both groups of animals.

Results and Discussion:

The number (M_n) and weight (M_w) average molecular weights were 49 kDa and 34 kDa for *Pol*$_1$, and 101 kDa and 49 kDa for *Pol*$_2$. Both conjugates were synthesized with PGA of similar molecular weight. However, *Pol*$_1$ has a smaller hydrodynamic volume after conjugation, possibly due to the aggregation of relatively hydrophobic Mce_6. Mce_6 content was 2.5 mol-% in *Pol*$_1$. Gd content for *Pol*$_1$ and *Pol*$_2$ was 20 and 29 mol-%, respectively. The T1 relaxivity was 8.46 and 8.33 mM^{-1}sec^{-1} for *Pol*$_1$ and *Pol*$_2$, respectively.

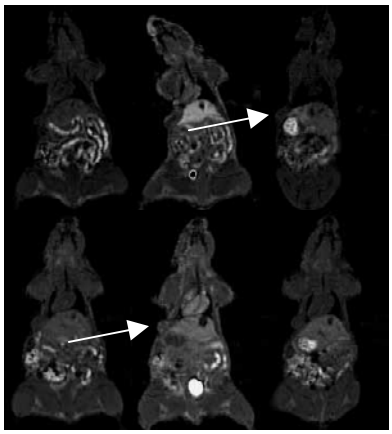

Fig. 1 (left). Coronal MR images of the mice through tumor before and at 1, and 18hrs after injection of *Pol*$_1$ (top) and *Pol*$_2$ (below), respectively.

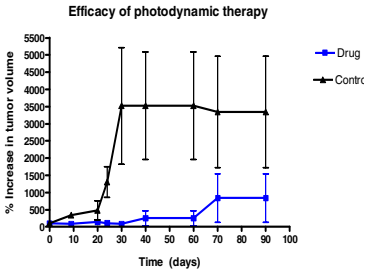

Fig. 2 (right). Tumor growth after the treatment with laser 18 and 24 hours after the injection of *Pol*$_1$ and *Pol*$_2$.

Significant contrast enhancement was observed in the tumor with both conjugates and the enhancement lasted at least for 18 hours, Figure 1, indicates tumor accumulation of the conjugates in the tumor tissue. Figure 2 shows the tumor response to photodynamic therapy. Significant therapeutic response was observed in the mice treated with PGA-(Gd-DOTA)-Mce_6 as compared to the mice treated with PGA-(Gd-DOTA). All of the mice (5 mice) treated with PGA-(Gd-DOTA)-Mce_6 survived 90 days after the treatment. Four mice (out of five mice) treated with PGA-(Gd-DOTA) died with 40 days after the treatment and only one mouse survived for 90 days. The results have demonstrated that the paramagnetically labeled polymeric drug delivery system for photodynamic therapeutics, PGA-(Gd-DTPA)-Mce_6, was able to deliver sufficient amount of contrast agent and photosensitizer to the solid tumor, resulting in visualization of the tumor, guiding the treatment with photodynamic therapy. Since a low light dose was used in the treatment and it only activated tumor tissue with drug accumulation, it caused little damage to normal tissue. The procedure is non-invasive and efficacious for cancer treatment.

Conclusions:

The paramagnetically labeled polymeric drug delivery system can effectively deliver both the contrast agent and therapeutic agent to solid tumor. Contrast enhanced MRI can accurately detect the solid tumor to guide the treatment with photodynamic therapy. Contrast enhanced MRI photodynamic therapy is effective for non-invasive and specific cancer treatment. It has a great promise to detect and non-invasively treat cancer at its earliest stage.

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