11C-methionine PET parametric response map, but not conventional MRI, corresponds to treatment response of WT1 immunotherapy for recurrent malignant glioma.

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Abstract

Immunotherapy targeting the Wilms' tumor 1 (WT1) gene product is a promising treatment modality for patients with malignant gliomas with reports of encouraging results [1]. It has become clear, however, that Gd-enhanced MRI (Gd-MRI) does not reflect prognosis, thereby necessitating a more robust imaging evaluation system for monitoring WT1 immunotherapy. In order to meet this demand, we have performed a voxel-wise parametric response map (PRM) analysis of ^{11}C-methionine PET (Met-PET) in WT1 immunotherapy and compared the data with the overall survival after WT1 immunotherapy initiation (OS_{WT1}). Fourteen recurrent malignant glioma patients were included and OS_{WT1} was compared with (1) volume and length change in contrast area of the tumor on Gd-MRI, (2) change in maximum uptake of ^{11}C-methionine (T/N max), and (3) a more detailed voxel-wise PRM analysis of Met-PET pre- and post-WT1 immunotherapy. PRM analysis was able to identify the following 3 areas within the tumor core: area with no change in ^{11}C-methionine uptake pre- and post-treatment (NC area), area with increased ^{11}C-methionine uptake post-treatment (PRM^{+Met}), and area with decreased ^{11}C-methionine uptake post-treatment (PRM^{-Met}). While Gd-MRI volumetric and conventional Met-PET analysis did not correlate with OS_{WT1} (p=0.270 for Gd-MRI length, p=0.960 for Gd-MRI volume, and p=0.110 for Met-PET), the percentage of PRM^{+Met} area showed excellent correlation (p=0.008) with OS_{WT1}. This study describes the limited value of Gd-MRI and highlights the potential of voxel-wise PRM analysis of Met-PET for monitoring treatment response in immunotherapy for malignant gliomas. As new treatment modalities are becoming available for malignant gliomas, limited value of Gd-MRI should be recognized in treatment such as immunotherapies.

Materials and Methods

WT1 immunotherapy

Patients received intradermal injections of 3.0 mg of modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant. The WT1 vaccinations were given weekly for 12 consecutive weeks. Twelve weeks after the initial vaccination, the response was evaluated by both MRI and Met-PET.

MRI / PET scans

All MR images were obtained using a 3.0-T (Signa, GE Medical Systems, Milwaukee, WI, USA) whole-body MR scanner. PET studies were performed on the Eminence instrument by Shimazu (Kyoto, Japan). ^{11}C-methionine (111 to 222 MBq; 3 to 6 mCi) was injected intravenously. Tracer accumulation was recorded over 15 minutes in 99 transaxial slices from the entire brain. Total activity from 20 to 35 minutes after tracer injection was used for image reconstruction.

Tumor length and volume measurement

Tumor length, corresponding to the contrast-enhanced area on T1-weighted MRI, was measured and analyzed according to RECIST Ver.1.0,. Tumor volume was measured by performing a 3-dimensional threshold-based volume-of-interest (VOI) analysis in all patients for contrast-enhanced lesions on Gd-MRI, using the ImageJ software.

Parametric Response Map calculation algorithm

As in **Figure 1**, Post-WT1 ^{11}C-methionine uptake was plotted as a function of Pre-WT1 ^{11}C-methionine uptake in both normal brain and gadolinium enhancing lesions. A linear regression fitting was applied to the data obtained by the ROI placed at the normal brain (**Figure 1**, blue line). Next, the magnitude of deviation of each data point (*i*) from the expected linear regression fitting was calculated as z-scores from the linear regression line. As a result, PRM is identical to the z-score of each data point in the lesion from the expected linear regression line calculated by the normal brain.

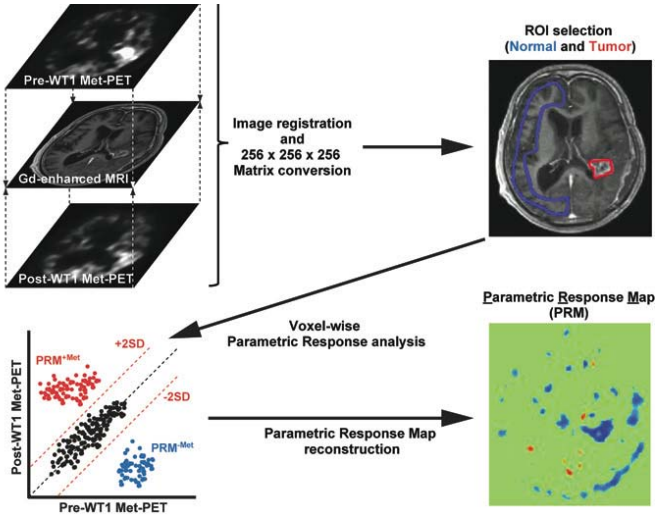

Fig. 1 ^{11}C-methionine PET data before and 12 weeks after WT1 immunotherapy initiation was fused and registered onto conventional contrast-enhanced MRI. All 3 images were converted into a 256 × 256 × 256, 1 mm isotropic image matrix. Post-WT1 ^{11}C-methionine uptake was plotted as a function of pre-WT1 ^{11}C-methionine uptake. After calculating the linear regression line with the ±2SD distribution range in contralateral normal brain tissue, a region of interest (ROI) was set at the contrast enhanced lesion pre-WT1 immunotherapy. The obtained plots were categorized into the following 3 areas: no change in ^{11}C-methionine uptake pre- and post-treatment (NC area), an area with increased ^{11}C-methionine uptake post-treatment (PRM^{+Met}), and an area with decreased ^{11}C-methionine uptake post-treatment (PRM^{-Met}). These areas were reconstructed in images for visual inspection (PRM^{+Met} in red and PRM^{-Met} in blue).

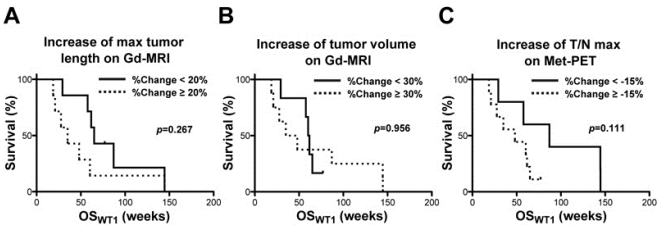

Fig. 2 None of the conventional MRI or PET analysis was able to correlate with OS_{WT1}.

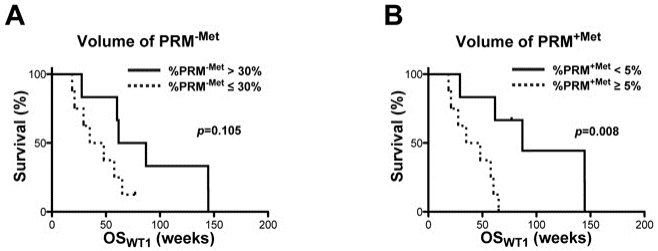

Fig. 3 PRM^{+Met} was able to be a predictive factor of WT1 immunotherapy in malignant glioma.

Results and Discussion

As in **Fig. 2**, we clearly showed that conventional MRI analysis failed to show any correlation with OS_{WT1}. Moreover, conventional ^{11}C-methionine PET analysis, which is based on analyzing the maximum uptake values, also failed to show correlation with OS_{WT1}. On the other hand, Fig. 3 shows that PRM^{+Met} with a threshold set at 5% was able to separate long survivors from treatment non-responders with a p value as low as 0.008. This statistical significance was still valid even after adjusting age and performance status, both of which are significant prognostic factors of glioblastoma. The above observation clearly shows that treatment response of malignant glioma by WT1 immunotherapy cannot be predicted by conventional Gd-MRI and that other modalities such as PRM analysis of ^{1}C-methionine PET is necessary for evaluating the effect of immunotherapies. This is also crucially important in designing clinical studies using novel treatment strategies against malignant gliomas.

References

1. Izumoto S et al. Phase II clinical trial of Wilms tumor 1 peptide vaccination for patients with recurrent glioblastoma multiforme. ***J Neurosurg.*** 2008 May;108(5):963-71.