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. It has become clear, however, that gadolinium-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 [11C]methionine PET (Met-PET) in WT1 immunotherapy and compared the data with the overall survival after WT1 immunotherapy initiation (OS-WT1). Twelve weeks after the initial vaccination, the response was evaluated by both MRI and Met-PET.

Materials and Methods

WT1 immunotherapy

Patients received intradermal injections of 50 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 Emisisence instrument by Shimazu (Kyoto, Japan). [11C]methionine (111 to 222 MBq; 5 to 6 mCi) was injected intravenously. Tissue accumulation was recorded over 15 minutes in 99 transaxial slices from the same brain. Total activity from 20 to 55 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 RCBCT 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 [11C]methionine uptake was plotted as a function of Pre-WT1 [11C]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.

Results and Discussion

As in Figure 2, we clearly showed that conventional MRI analysis failed to show any correlation with OS-WT1. Moreover, conventional [11C]methionine PET analysis which is based on analyzing the maximum uptake values also failed to show correlation with OS-WT1. On the other hand, Figure 3 shows that PRM 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 [11C]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