Discriminating Depth of Response to Therapy in Multiple Myeloma Using Whole-body Diffusion-weighted MRI with Apparent Diffusion Coefficient:
Preliminary Results From a Single-center Study

Chao Wu, MD, Juan Huang, MD, Wen-Bin Xu, MD, Yong-Jing Guan, MD, Hua-Wei Ling, MD,
Jian-Qing Mi, MD, Hua Yan, MD, PhD

Rationale and Objectives: This study aimed to measure apparent diffusion coefficient (ADC) in Chinese patients with newly diagnosed multiple myeloma by whole-body diffusion-weighted magnetic resonance imaging (WB-DWI MRI) and assess the diagnostic accuracy of ADC in the discrimination of deep response to induction chemotherapy.

Materials and Methods: Seventeen patients underwent WB-DWI MRI before and after induction chemotherapy (week 20). DWI images and ADC maps were produced and 89 regions of interest were chosen. ADC percent changes were compared between deep (complete response or very good partial response) and non–deep responders (partial response, minimal response, stable disease, or progressive disease) as International Myeloma Working Group criteria. Diagnostic accuracy of ADC was calculated using specific cut offs. Predictive positive value of ADC was calculated to predict deep response to consolidation therapy.

Results: Lesions reduced in size and number and signal intensity decreased in follow-up DWI, which did not differ between deep and non–deep responders. ADC percent changes were significantly higher in deep responders (36.79%) than in non–deep responders (11.50%) after induction therapy ($P = .02$) in per lesion analysis. ADC percent increases by 46.96%, 78.0% yielded specificity at 81.4%, 90.7% in discriminating deep response to induction therapy. Predictive positive value predicting deep response to consolidation therapy was 60.5% by using ADC cutoff $>1.00 \times 10^{-3}$ mm^2/s at week 20.

Conclusions: ADC from WB-DWI MRI increased remarkably in patients who achieved deep response at the end of induction chemotherapy, which represented a confirmatory diagnostic tool to discriminate deep response to induction therapy for patients with multiple myeloma. ADC may have a potential to predict deep response to consolidation therapy.

Key Words: Multiple myeloma; depth of response; whole-body diffusion-weighted MRI; apparent diffusion coefficient.

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy characterized by clonal proliferation of plasma cells, which may produce excessive amounts of monoclonal immunoglobulins. MM accounts for 10%–15% of all hematologic malignances and results in 15%–20% deaths (1–3). With the introduction of novel therapeutics including immunomodulatory agents (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib), the prognosis of patients with MM has significantly improved. Recent studies have confirmed the significance of deep response particularly complete response (CR) or very good partial response (VGPR) to induction therapy for patients with newly diagnosed MM (4–6).

On the other hand, methods for evaluating treatment response still remain scarce and existing ones have limitations. Serum or urine measurements (M-proteins, free light chain) are part of clinical assessment but lack reliability in nonsecretory MM. Bone marrow biopsy is invasive, and sampling errors may occur because of scattered bone lesions (7). Conventional radiographs provide morphologic information and are still the primary choice for response assessment and follow-up in MM (2,8). However, functional changes in lytic bone lesions cannot easily be captured by conventional radiology, even after an effective therapy (9), causing difficulty in the discrimination of treatment response in MM. More advanced techniques, including positron emission tomography-computed tomography, may be clinically limited by higher cost and radiation exposure.

Among all imaging techniques, magnetic resonance imaging (MRI) remains the most sensitive and specific for the detection of bone marrow infiltration before the appearance of osteolytic lesions (10). The detection rate and overall performance of MRI could be enhanced by using functional MRI techniques, such as diffusion-weighted imaging (DWI) (11). Whole-body diffusion-weighted MRI (WB-DWI MRI) is a new functional imaging technology that evolved from conventional MRI sequences and is currently the only noninvasive technique reflecting diffusion of water molecules in human tissues. WB-DWI MRI, which combines DWI-MRI with short-time inversion recovery and echo planar imaging sequences, can quantitatively measure the diffusion of water molecules between intra- and extracellular spaces by apparent diffusion coefficient (ADC), a quantitative parameter of DWI signal intensity (SI) (12–16). ADC has been demonstrated to distinguish bone marrow differences between patients with active myeloma and those in remission (17).

A few studies explored the association between ADC and treatment response and showed the feasibility of assessing treatment response by using WB DWI-MRI in patients with MM (17–20). But clinical evidence on the association between ADC levels and achieving deep response to induction therapy is lacking in MM. Our study aimed to explore the ADC changes by WB DWI-MRI and its diagnostic and predictive roles in discriminating deep response to induction and consolidation therapy in Chinese patients with newly diagnosed MM.

MATERIALS AND METHODS

Study Design

This study was designed to prospectively collect ADC and clinical data from patients newly diagnosed with MM in a single center between January 2015 and June 2016. WB DWI-MRI was performed at treatment initiation (baseline) and the end of induction treatment (week 20, four cycles of standard chemotherapy), respectively. All patients were treated with a standard bortezomib-based chemotherapy protocol (with dexamethasone plus lenalidomide, doxorubicin, or cyclophosphamide) for induction therapy. Patients were followed up until the end of consolidation therapy. The options of consolidation therapy were bortezomib-based chemotherapy protocol or autologous hematopoietic stem cell transplantation. WB DWI-MRI images were evaluated independently by two experienced radiologists (J.H. and Y.J.G.) who were blinded to the patient's clinical information. A third senior radiologist (H.W.L.) would adjudicate the final result if there was a disagreement in conclusions between the two radiologists.

Patient

Patients were eligible if they were above 18 years of age inclusive and hospitalized to the hematology department, had a definite diagnosis of primary active MM based on criteria of International Myeloma Working Group (21), and consented to have WB-DWI MRI and the study. Patients were excluded if they had comorbid malignancies, ineligible MRI examination (eg, claustrophobia, metallic implants), or other clinical circumstances precluding the inclusion into the study at the investigator's discretions. All authors are the study investigators and thus had the access to patient's personal identifiers for the purpose of study treatment and follow-up.

The study was conducted in accordance with the guidelines of the International Conference on Harmonization and was approved by Ethics Committee of Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Patients were screened in the inpatient department, and written informed consent was obtained from all patients before screening.

Image Acquisition and Analysis

WB-MRI examinations were performed on a GE Signa HDxt 1.5T WB magnetic resonance scanner and achieved by the cross-sectional scanning. All 17 patients underwent WB DWI-MRI scanning with short-time inversion recovery and echo planar imaging sequences. The patient was scanned supine with elevation of the neck, the lumbosacral, and the leg, ranging from the head to the knees divided into seven sections with