Dynamic contrast-enhanced magnetic resonance imaging for assessment of anti-angiogenic treatment effects in multiple myeloma

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Running head: DCE-MRI in multiple myeloma

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Abstract

Purpose: To non-invasively assess bone marrow microcirculation before and after therapy in patients with newly diagnosed multiple myeloma (MM) with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Methods: 96 patients received DCE-MRI before and after primary treatment for newly diagnosed MM. For the 91 evaluable patients, treatment consisted of high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) in 82 patients and chemotherapy without ASCT in 9 patients. Additionally, 33 healthy volunteers were imaged as control group. Analysis of DCE-MRI was performed according to the two-compartment model by Brix to quantify amplitude A (associated with blood volume) and exchange rate constant kep (reflecting vessel permeability and perfusion).

Results: Non-responders showed significantly higher A-values before the start of therapy compared to responders (p=0.02). In both, responders and non-responders to therapy, A-values dropped significantly (p=0.004 and <0.001, respectively) after primary therapy while lower values for kep were only found in responders (p<0.001). Depth of remission was significantly correlated to decreased bone marrow microcirculation: Patients in near complete (nCR) or complete remission (CR) after treatment showed significantly lower values for A compared to patients not achieving nCR+CR. The application of HDT or novel agents had no significant effect on DCE-MRI parameters after therapy, although patients treated with novel agents achieved more often nCR+CR (42%/12.5%;p<0.002). Higher kep-values at 2nd MRI were positively correlated to shorter overall survival (HR 3.53; 95% CI 1.21,10.33; p=0.02).

Conclusion: Parameters from DCE-MRI are correlated to remission after primary therapy and outcome in newly diagnosed MM.
Statement of translational relevance:

Angiogenesis has been identified as a pathogenic and prognostic factor in multiple myeloma. DCE-MRI is a non-invasive imaging method quantifying bone marrow microcirculation in patients with plasma cell diseases. Our study demonstrates that DCE-MRI enables the assessment of anti-angiogenic treatment effects to primary therapy in patients with MM. We showed that patients in remission exhibit significantly decreased A- and $k_{ep}$-values, which are surrogate markers for decreased bone marrow microcirculation. Furthermore, non-responders exhibited higher baseline A-values than responders and higher $k_{ep}$-values after therapy are associated with shorter overall survival. Imaging treatment response in multiple myeloma nowadays is mainly based on the assessment of morphological changes upon therapy. Since morphological changes - especially of osteolysis - rarely occur shortly after therapy, DCE-MRI is useful for imaging early treatment response in multiple myeloma.
Introduction

In multiple myeloma (MM) the interaction between malignant plasma cells and non-malignant stromal cells causes several changes in the bone marrow microenvironment that are pivotal for the pathogenesis of the disease. The induction of angiogenesis by malignant plasma cells plays a major role in the transformation from non-malignant precursor states like monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) to symptomatic MM (1, 2). Correspondingly, patients with MM show a higher bone marrow microvessel density (MVD) than patients with SMM, MGUS or healthy individuals (3). Increased bone marrow microcirculation is associated with adverse outcome in patients with MM (4, 5) as well as SMM (6), and angiogenesis is directly linked to the development of MM-related bone disease (7, 8). Furthermore, patients in remission after therapy showed a significantly decreased MVD compared to those with residual disease (9-11). In most of these studies histological evaluation of bone marrow biopsies was performed to quantify angiogenesis. However, bone marrow biopsies are obtained from a small anatomical region and will not be repeated unless clinically indicated. Therefore, there are only limited data available on how bone marrow microcirculation changes over time in patients with MM receiving systemic therapy.

Imaging treatment response in MM is an important but challenging task since lytic bone lesions only undergo subtle morphological changes after treatment (12). Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive imaging modality to study bone marrow microcirculation in patients with monoclonal plasma cell diseases (6, 13-15). In patients with solid tumors it has become a valuable tool to quantify treatment response beyond measuring tumor size. However, there are only few studies including small numbers of heterogeneous
patient groups that used DCE-MRI for the longitudinal assessment of anti-angiogenic treatment response in MM (16, 17). We therefore performed this prospective trial applying DCE-MRI in patients before and after therapy under the hypothesis that changes in bone marrow microcirculation are correlated to remission and outcome in newly diagnosed MM. Furthermore, we investigated whether baseline parameters from DCE-MRI might predict treatment response.
Patients and Methods

Patients

After written informed consent, 96 patients with newly diagnosed MM were recruited between November 2004 and April 2011 to receive DCE-MRI before the start of systemic treatment and after the first-line of therapy. The study was approved by the institutional ethics committee. No prior systemic therapy for MM was allowed before the 1st DCE-MRI. 5 patients had to be excluded from the analysis for they had been assigned to second-line treatment before second MRI because of progression during first-line therapy. Patient characteristics at 1st DCE-MRI are summarized in Table 1. Median time from 1st to 2nd MRI was 14 months. There were three patients with > 30 months from 1st to 2nd MRI. They were included in the analysis because they remained in remission and did not receive further therapy beyond first-line treatment. Additionally, 33 healthy individuals (16 female, 17 male, median age 56 years) were included in our study as control group after written informed consent was obtained.

Imaging protocol and analysis

MRI was performed on a 1.5 Tesla MRI (Magnetom Symphony, Siemens Medical Solution, Erlangen, Germany) equipped with a spine coil for radiofrequency excitation and detection as described previously (6). For DCE-MRI, we used a saturation recovery TurboFLASH-Sequence in sagittal orientation covering the lumbar spine (TR/TE 79/4.76 ms, FOV 380 mm, 9 slices, 8 mm slice thickness, voxel size 1.5 x 1.5 x 8 mm, flip angle 80°, total acquisition time: 5 min 54 s). After the first 4 measurements, 0.1 mmol/kg Gadolinium-DTPA (Magnevist, Bayer Schering Pharma, Berlin, Germany) were intravenously infused via a cannula placed in an antecubital vein with an automated injection system (Spectris Solaris, Medrad, Volkach,
Image post-processing and analysis was performed according to the two-compartment model proposed by Brix et al. with the MeVislab software (MeVis Medical Solutions AG, Bremen, Germany) to calculate amplitude $A$ (arbitrary units, a.u.) and exchange rate constant $k_{ep}$ (min$^{-1}$) (18). In the Brix model, amplitude $A$ is mainly influenced by the distribution space of the contrast agent and therefore a surrogate for blood volume, while $k_{ep}$ reflects both, vessel permeability and perfusion (19). Pixel-based analysis of both parameters was performed in manually selected regions of interest (ROIs). Investigators were blinded to patients’ remission and outcome. To minimize inter-observer variability, the selected ROIs contained the whole bone marrow of lumbar vertebral bodies that was identified on unenhanced T1-weighted images. In that way, values of 455 vertebral bodies were assessed before and after therapy. Since degenerative changes like osteochondrosis, Schmorl’s nodes or anatomical variants like a prominent basivertebral vein can cause changes that might mimic plasma cell infiltration, these structures were not included in the respective ROIs. Overall 21 vertebral bodies had to be excluded from the analysis because of these changes. The Brix model was applied since it had been shown to be more robust than the also established model proposed by Tofts and colleagues (19).

**Treatment**

High-dose therapy (HDT) followed by autologous blood stem cell transplantation (ASCT) was performed in 82 patients. Single HDT was performed in 39 cases, while 43 patients received tandem HDT. Patients treated with HDT received a median of 3 cycles (range 2-4) induction chemotherapy consisting of either vincristin (VAD, n=34 patients), bortezomib (PAD, n=34) or thalidomide (TAD, n=10) in combination with
adriamycin and dexamethasone. In one patient receiving bortezomib as induction therapy, adriamycin was replaced by cyclophosphamide, 2 patients received only adriamycin/dexamethasone and one patient was treated with ifosfamide/dexamethasone before HDT. In patients, who were candidates for HDT, induction therapy was followed by a cycle of cyclophosphamide, adriamycin and dexamethasone (CAD) as mobilization chemotherapy and G-CSF application for peripheral stem cell harvest. In one patient ifosfamide was used as mobilization chemotherapy and in another patient an antagonist against CXCR4 was used for stem cell mobilization. Out of 9 patients who were not eligible for HDT, 8 were treated with melphalan/prednisone (MP) alone (n=3), in combination with bortezomib (n=4) or thalidomide (n=1). One patient, not eligible for HDT, received 3 cycles VAD followed by 2 cycles Bortezomib/dexamethasone. Table 1 gives a summary of the applied chemotherapy.

Follow-up
All patients were seen in our outpatient clinic every 3-6 months after the initial diagnosis, including physical examinations, routine blood work, serum electrophoresis and urine analysis. For HDT with ASCT, patients were admitted to our ward. After discharge, patients presented again in our outpatient clinic for assessment of treatment response according to the guidelines of the International Myeloma Working Group (IMWG) and for the second DCE-MRI. IMWG response criteria were modified to include near complete response (nCR). Patients were stratified into three groups according to how they had responded to therapy: Group 1 = near complete response and complete remission (nCR+CR). Group 2 = very good partial remission, partial remission or minimal response (VGPR+PR+MR). Group 3 =
stable disease or progressive disease (SD+PD). Patients in group 1 and 2 were considered responders to therapy; patients in group 3 were classified as non-responders.

**Statistical analysis**

Fisher’s exact test was used to compare remission rates according to applied therapies. A- and k\textsubscript{ep}-values of ROIs from the 5 vertebral bodies of the lumbar spine were summarized for each patient as median values. Median k\textsubscript{ep}-values were log-transformed before the analysis. Since previous studies showed that k\textsubscript{ep} values can only be determined reliably for values ≤13 min\textsuperscript{-1}, values > 13 min\textsuperscript{-1} were truncated at 13 min\textsuperscript{-1}. To assess changes in DCE-MRI parameters A and k\textsubscript{ep} before and after therapy for responders and non-responders, the paired Wilcoxon signed-rank test was performed. The distribution of median A- and k\textsubscript{ep}-values was compared between the different remission categories using Wilcoxon rank sum tests. Differences and trends for A and k\textsubscript{ep} in the remission categories after therapy were analyzed using the Kruskal Wallis test and the Jonckheere Terpstra trend test. Multivariate linear models accounting for baseline DCE-MRI values at 1\textsuperscript{st} MRI, the application of novel agents and HDT were used to analyze the impact of these factors on the change of A/k\textsubscript{ep} between the 1\textsuperscript{st} and 2\textsuperscript{nd} DCE-MRI. Furthermore, multivariate logistic regression models were applied for modeling dichotomized response to therapy in dependency of baseline A/k\textsubscript{ep}-values at 1\textsuperscript{st} MRI, changes in A/k\textsubscript{ep}-values between 1\textsuperscript{st} and 2\textsuperscript{nd} MRI as well as the application of novel agents and HDT. Cox models were fitted to investigate the prognostic value of median A/k\textsubscript{ep} at the 2\textsuperscript{nd} MRI for progression-free (PFS) and overall survival (OS). PFS and OS were calculated starting from time of the 2\textsuperscript{nd} MRI. P-values < 0.05 were considered statistically significant. Data analysis
was performed using SPSS 20 (IBM, Armon, NY) and R versions 2.15.3 and 3.1.1 (http://cran.r-project.org/).
Results

Response to treatment

Out of the 91 patients, 26 patients (29%) had achieved nCR+CR at the time point of the 2nd MRI and 55 patients (61%) achieved MR, PR or VGPR. Therefore, 81 patients (90%) were considered as responders to therapy, while 9 patients showed stable or progressive disease at the second DCE-MRI and were classified as non-responders. In one patient with non-secretory MM the remission after primary therapy could not be defined according to IMWG criteria. Rates of nCR+CR were not significantly different between patients eligible (28.4 %) or not eligible for HDT (33.3%, p=0.80). Patients - either eligible or not eligible for HDT – that were treated with thalidomide or bortezomib achieved significantly more often nCR+CR (42.0%) compared to patients treated with neither of these agents (12.5%, p=0.002). Remission after primary therapy is summarized in Table 1.

DCE-MRI parameters before and after treatment in responders and non-responders to therapy

Non-responders showed significantly higher median values for amplitude A before the start of treatment compared to responders to therapy (p=0.02, Figure 1A). No significant differences between the two groups were found for median exchange rate constant $k_{ep}$ before therapy (p=0.52, Figure 1B). In non-responders to therapy, the second DCE-MRI revealed a significantly lower median amplitude A compared to initial values (p=0.004, Figure 1A), while no significant changes were found for median $k_{ep}$-values (p=0.20, Figure 1B). The observed effects on A and $k_{ep}$ were more pronounced in patients responding to therapy: Responders showed significantly
lower median values for A (p < 0.001, Figure 1A) and k_{ep} (p<0.001, Figure 1B). Figure 1 depicts all measured DCE-MRI values.

**DCE-MRI parameters after treatment according to remission after therapy**

The comparison of DCE-MRI parameters from patients in nCR+CR after therapy with patients achieving VGPR+PR+MR or with patients not responding to therapy revealed the following differences among the groups (Figure 2): Patients in nCR+CR showed significantly lower median A-values after treatment compared to patients with VGPR+PR+MR (p=0.012) and SD+PD (p=0.03) since median values dropped to same levels as in healthy individuals (Figure 2A, respectively). Additionally, patients with SD+PD had higher median A-values after therapy than patients in VGPR+PR+MR (p<0.001, Figure 2A). No significant differences were found for median exchange rate constant k_{ep} among the three different groups (Figure 2B). Jonckheere Terpstra trend tests, which examine the association of ordered categorical response with the median DCE-MRI values at 2^{nd} MRI showed a significant association with median A-values at 2^{nd} MRI (p=0.003). When testing the association between values measured at the second DCE-MRI and the application of HDT or thalidomide and bortezomib, no significant results were obtained.

**Multivariate analysis of DCE-MRI parameters and response**

Multivariate linear models demonstrated that neither the application of novel agents nor HDT had a significant impact on changes in median A/k_{ep}-values between the 1^{st} or 2^{nd} MRI. Higher median A/k_{ep}-values at 1^{st} MRI were significantly associated with smaller changes between the 1^{st} and 2^{nd} DCE-MRI (p<0.001, respectively).
In the multivariate logistic regression model of dichotomized response including median A-values at 1\textsuperscript{st} MRI and change in median A-values, the application of tandem HDT was the only significant prognostic factor (p=0.01; Odds Ratio (OR): 14.1; 95% confidence interval (CI): [1.5,130.2]). However, a negative trend of higher median A-values at 1\textsuperscript{st} MRI on response to therapy was observed (p=0.08; OR: 0.4; 95% CI: [0.1,3.2]).

In the multivariate logistic regression model including log-transformed median k\textsubscript{ep}-values at 1\textsuperscript{st} MRI and change in log-transformed median k\textsubscript{ep}-values, the only prognostic factor was application of tandem HDT as well (p=0.006; OR: 15.6; 95% CI: [1.9,128.8]).

**Survival analysis**

Median follow-up was 39.0 months with a median PFS of 20.1 months after 2\textsuperscript{nd} MRI. Median OS was not reached. Survival analysis revealed, that higher median k\textsubscript{ep}-values at the 2\textsuperscript{nd} MRI resulted in shorter OS (HR 3.53; 95% CI 1.21,10.33; p=0.02). These changes were also associated with shorter PFS but did not reach statistical significance (HR 1.37; 95% CI 0.85,2.18; p=0.19). No significant results were obtained for amplitude A.
Discussion

In our current prospective study we performed DCE-MRI before and after primary therapy in patients with newly diagnosed MM to longitudinally assess changes in bone marrow microcirculation and correlate findings with treatment response. We demonstrate for the first time that responders exhibit significantly lower values for amplitude $A$ and exchange rate constant $k_{ep}$ compared to non-responders after therapy and higher $k_{ep}$-values after therapy are associated with shorter OS. Furthermore, depth of remission was significantly correlated to lower $A$-values and patients not responding to therapy showed higher $A$-values before the start of therapy compared to responders. Previous studies indicated that the induction of angiogenesis is crucial for the progression from MGUS and SMM to symptomatic MM (1, 3) and response to treatment is accompanied by decreased MVD (9-11). We non-invasively confirmed these findings and showed that a reduction of tumor burden is not only accompanied by drop of blood volume (lower $A$-values), but also reduced vessel permeability (lower $k_{ep}$-values). This is in line with preclinical and clinical studies in solid tumors demonstrating that anti-angiogenic treatment effects are not only limited to vessel regression but also functional normalization of tumor vasculature (20).

Since the introduction of thalidomide, bortezomib and lenalidomide it has been argued whether the improved outcome compared to conventional chemotherapy might be due to the anti-angiogenic properties of the respective agents (21). In the case of immunomodulatory drugs, anti-angiogenesis has been described as one of the versatile effects on the bone marrow microenvironment (22). Bortezomib exhibited anti-angiogenic properties in preclinical studies as well (23). A remaining
question is, whether vessel regression upon therapy is due to anti-angiogenic therapy effects or just an epiphenomenon of successful myeloma treatment. In our current study, treatment with novel agents or tandem HDT improved remission compared to conventional chemotherapy but was not associated with lower DCE-MRI parameters in multivariate analysis. Since depth of remission was associated with lower A-values after primary therapy, we suppose that the observed normalization of microcirculation in patients achieving nCR+CR might have been rather a consequence than a prerequisite for successful treatment. In line with these results we found also in non-responders lower A-values after therapy compared to the initial measurements which might indicate that vessel regression alone does not automatically translate into reduction of tumor burden. Although this assumption needs to be clarified by further studies, recent clinical trials with anti-angiogenic monoclonal antibodies or tyrosine kinase inhibitors as single agents or in combination with bortezomib as well as lenalidomide failed to show additional benefit in patients with relapsed or refractory MM (24-27).

Beyond the observed correlation between bone marrow microcirculation and remission after therapy we found that non-responders had significantly higher baseline A-values than responders. Additionally, in patients with higher baseline A/kep-values the treatment-induced drop was less pronounced than in patients with lower baseline values. Therefore, DCE-MRI before the start of therapy might have predictive and prognostic implications. This assumption is supported by a recent study, which demonstrated that pro-angiogenic factors lead to drug resistance and relapse in MM patients (28).
Imaging treatment response in MM is challenging because morphological changes of existing bone lesions seldom occur after therapy (29). With our study we were able to assess treatment response based on quantitative parameters, which is less influenced by inter-observer variability than morphological evaluation of osteolyses. This is of particular interest for the assessment of treatment response in non-secretory myeloma or patients with extramedullary disease. Additionally, DCE-MRI might also help to detect viable tumor tissue within preexisting ostelyoses and to identify candidates for local therapy. This theory is supported by findings from a small study that linked high values for amplitude A to increased fracture risk during follow-up (30). Furthermore, DCE-MRI offers the opportunity to image treatment response in asymptomatic patients without osteolyses which might become attractive in the future with the emerging role of treating patients with high-risk SMM (31).

There are major downsides to the current study that need to be addressed in future trials of DCE-MRI in MM. To investigate early treatment effects, follow-up examinations with DCE-MRI need to be scheduled at earlier time-points and not only at the end of primary therapy as in the current study. This might clarify if changes in bone marrow microcirculation precede or just parallel the reduction of tumor burden. Since recruitment for this trial started in 2004 and ended in 2011, patients enrolled at later time points were more likely to be treated with novel agents during induction therapy. This might have influenced the prognostic evaluation of DCE-MRI on PFS and to a lesser degree on OS, since novel agents were already available for treatment of relapsed disease in 2004. Additionally, the prognostic value of DCE-MRI in MM needs to be confirmed in a larger cohort of patients, not only with symptomatic disease but also MGUS and SMM.
In summary we demonstrate that longitudinal assessment of bone marrow microcirculation with DCE-MRI correlates with treatment response in MM and has prognostic implications in newly diagnosed patients.
Figure legends

**Figure 1** Boxplots of DCE-MRI parameters $A$ and $k_{ep}$ before and after primary therapy for responders and non-responders. The box depicts the interquartile range with the median value as line. Whiskers show 10$^{th}$ and 90$^{th}$ percentiles and outliers are depicted separately. The symbol ‘*’ denote significant differences between the groups.

**Figure 2** Boxplots of DCE-MRI parameters $A$ and $k_{ep}$ according to remission after primary therapy and for healthy individuals (controls). The box depicts the interquartile range with the median value as line. Whiskers show 10$^{th}$ and 90$^{th}$ percentiles and outliers are depicted separately. The symbol ‘*’ denote significant differences between the groups.

**Figure 3** Representative color maps for parameters $A$ and $k_{ep}$ before and after successful primary therapy. Values range from high (red) to low (blue).
Table 1 Patients characteristics, overview over treatment and response to primary therapy, *LDH* – lactate dehydrogenase, *HDT* – high dose therapy

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References


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