Changes in magnetic resonance imaging before and after autologous stem cell transplantation correlate with response and survival in multiple myeloma

Jens Hillengass,[1,2]* Sofia Ayyaz,[1]* Kerstin Kilk,[3] Marc-André Weber,[3] Thomas Hielscher,[4] Rajiv Shah,[2] Dirk Hose,[1] Stefan Delorme,[2] Hartmut Goldschmidt,[1,5] and Kai Neben[1]

[1]Department of Internal Medicine V, University of Heidelberg; [2]Department of Radiology, German Cancer Research Centre, Heidelberg; [3]Department of Diagnostic and Interventional Radiology, University of Heidelberg; [4]Department of Biostatistics, German Cancer Research Centre, Heidelberg; and [5]National Centre for Tumour Diseases, Heidelberg, Germany

ABSTRACT

In multiple myeloma, focal lesions, as well as diffuse and variegated infiltration patterns, can be detected by magnetic resonance imaging. In the current study, we compared treatment response in 100 myeloma patients with changes in infiltration patterns in whole body magnetic resonance imaging before and after autologous stem cell transplantation. We found an agreement between serological response and changes in imaging (P<0.001). In detail, a significant agreement of treatment response was observed for diffuse (P=0.004) as well as for focal (P=0.01) infiltration patterns. The number of focal lesions at second magnetic resonance imaging was of prognostic significance for overall survival (P=0.001). We conclude that treatment response in myeloma goes along with a decrease in imaging findings. We suggest that residual disease after high-dose chemotherapy detected by magnetic resonance imaging increases the risk of relapse. Therefore, myeloma patients with such findings after treatment might benefit from further cytoreduction.

Key words: mixed-phenotype acute leukemia, immunophenotype, cytogenetic, mutation, therapy.

Citation: Hillengass J, Ayyaz S, Kilk K, Weber M-A, Hielscher T, Shah R, Hose D, Delorme S, Goldschmidt H, and Neben K. Changes in magnetic resonance imaging before and after autologous stem cell transplantation correlate with response and survival in multiple myeloma Haematologica 2012;97(11):1757-1760. doi:10.3324/haematol.2012.065359

Introduction

In multiple myeloma (MM), the introduction of novel agents has improved the quality of response, especially after high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). The parameters defining the international uniform response criteria (IURC) are primarily monoclonal protein and bone marrow infiltration of myeloma cells.[1] However, since magnetic resonance imaging (MRI) studies in patients with MM have demonstrated that 18-50% of them present with focal lesions (FL),[2-4] it is likely that unilateral biopsy of the iliac crest for histological and aspiration-based examinations misses accumulations of myeloma cells located elsewhere in the body.

A promising extension of the current diagnostic tools for assessment of tumor mass and treatment response is, therefore, the application of novel imaging techniques. Whole body magnetic resonance imaging (wb-MRI) has been proven to be the best available imaging method to display bone marrow infiltration in patients with MM with regard to sensitivity and proportion of the body displayed.[5-7] Wb-MRI is able to detect and to monitor tumor mass of MM independently of the secretory activity and the location of the malignant cells. In patients with monoclonal plasma cell disease, FLs and diffuse infiltration detected by MRI are significant prognostic markers for progression free and overall survival.[8-11] Until now, it has not been clear whether the assessment of remission can be matched with changes in MRI. Also, it has not yet been clarified whether residual changes in bone marrow such as FLs may be the source of disease relapse. Therefore, the aim of the present study was to compare remission of disease with changes in wb-MRI and to investigate the prognostic significance of residual bone marrow infiltration.

Design and Methods

Patient cohort

We retrospectively evaluated a series of 100 consecutive patients with MM from a single institution who had undergone wb-MRI at the onset of therapy between October 2004 and July 2010, as well as 3-6 months after ASCT. Time between first MRI and initiation of systemic treatment was 0.4 months (range 0-3.9) and between ASCT and second MRI 5.6 months (range 0.4-39.3), respectively. The study group consisted of 58 males and 42 females with a median age of 58 years at first wb-MRI (range 28-73). All patients underwent one (n=45) or two (n=55) cycles of front-line high-dose chemotherapy with melphalan 200 mg/m^2 followed by ASCT according to the protocols of the GMMG-HD3 or GMMG-HD4 trial or analogous protocols.[12] For response assessment the IURC were used.[1] To simplify, IURC remission was determined summarizing very good partial

*JH and SA contributed equally to this study.

Funding: this study was in part supported by grants of the Dietmar-Hopp-Stiftung and the Deutsche Forschungsgemeinschaft (SFB Transregio 79).
Manuscript received on February 29, 2012. Revised version arrived on April 30, 2012. Manuscript accepted on May 22, 2012.
Correspondence: Jens Hillengass, M.D., Department of Internal Medicine V, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. Phone: international +49.6221568001. Fax: international +49.6221565721. E-mail: Jens.Hillengass@med.uni-heidelberg.de

remission (VGPR) and partial remission (PR) as seroPR. Study approval was obtained from the institutional review board of the University of Heidelberg.

MRI-protocol and evaluation

All patients underwent an MRI-protocol as reported recently.[5,9] No contrast medium was given. Number of FL, as well as degree of diffuse infiltration before and after treatment, was assessed by two investigators in consensus (SA and KK) for each time point separately. At time of second MRI, the investigators were blinded to the IURC-defined response of the patients. MRI response was assessed separately for diffuse and focal infiltration, and for the combination of both patterns. MRI response according to the change in the number of FL was defined as focal complete remission (fCR) indicating total disappearance of FL, focal partial remission (fPR) being defined as reduction in the number of FL of 50% or more, focal stable disease (fSD) as reduction of less than 50% of the number of FL or no change and focal progressive disease (fPD) as any increase in number of FL after therapy. For diffuse infiltration, dCR was defined as total disappearance of diffuse infiltration. If diffuse infiltration represented by bone marrow cellularity in MRI was reduced to any degree after therapy but was still detectable in MRI compared to a normal bone marrow signal, it was defined as dPR. Constancy of diffuse infiltration was defined as dSD and increase in diffuse infiltration as dPD.

To analyze association of IURC response and combined focal and diffuse MRI response, IURC response was aggregated into 'response' (seroPR or better), 'stable disease' (seroSD) and 'progressive disease' (seroPD). Focal and diffuse MRI assessments were also combined ('overall MRI response') into 'response' (dPR or better; fPR or better or response in both categories), 'stable' (fSD and dSD) and 'progressive' (fPD and/or dPD).

Statistical analysis

Agreement between MRI response and IURC response were assessed with the weighted Cohen's Kappa coefficient using Fleiss-Cohen weights including 95% confidence interval. Fisher's exact test was used to compare response distribution between treatments. Log rank test was used to determine prognostic impact of number of FL (0; 1-10; 11-20; >20) on survival, and distribution of survival times was estimated with the Kaplan-Meier method. Overall survival was defined as time from second MRI to death from any cause, and progression free survival (PFS) as time from second MRI to progression of disease or death, whichever occurred first. Patients who were seroPD at second MRI were excluded for PFS. All tests were two-sided; $P<0.05$ was considered statistically significant. All analyses were carried out with R 2.13.1 statistical software.

Results and Discussion

Response to treatment

MRI gains increasing significance in the diagnostic workup of patients with monoclonal plasma cell disease[13] because this technique has been demonstrated to have a higher sensitivity for the detection of bone marrow infiltration by myeloma cells compared to skeletal X-ray and computed tomography.[6,14] However, little is known about the changes seen in MRI after systemic treatment of MM, and especially the correlation of changes in serological markers and tumor mass detected by MRI. The present study is the first to investigate the correlation of IURC-derived and MRI response. Furthermore, we investigated the prognostic significance of FL before systemic treatment and after ASCT in a homogeneous group of 100 patients.

For the entire group of patients, the median PFS since second wb-MRI was 24.5 months (95% CI: 19.3 to NA), and the OS rate after 36 months 75%. At second wb-MRI, 11 patients were in CR, 74 patients in PR, 7 patients in SD and 8 patients in progressive disease based on the IURC for MM. The time span between first and second MRI varied between 6 and 45 months in our retrospective cohort; however, the time interval itself was not a prognostic factor based on Cox's regression models. Infiltration patterns at first and second MRI are summarized in Table 1.

Correlation of treatment response and MRI changes

IURC and MRI derived response rates as described above are listed in Table 2. The analysis of the association of IURC and imaging response revealed a weak agreement of focal response (kappa coefficient=0.25; 95% CI: 0.05-0.45; $P=0.01$) and a slightly stronger agreement of diffuse response (kappa coefficient = 0.26; 95% CI: 0.09-0.44; $P=0.004$) with IURC remission, respectively.

Comparison of MRI and IURC response revealed a trend to an underestimation of response for the focal and an overestimation compared to IURC response for the diffuse category. The kappa coefficient of the overall MRI response was 0.32 (95% CI: 0.15-0.49) ($P<0.001$). There was no agreement of MRI CR and seroCR.

In summary, a weak but significant agreement of IURC-derived and MRI-derived response was detectable and diffuse MRI response correlated better with the change of serological markers. This may be due to the fact that there seems to be a pathophysiological difference between a focal and a diffuse infiltration pattern. First references to this were identified by the Arkansas group who found differences of plasma cells of FL and those from random samples.[15] Furthermore, a connection of diffuse infiltration pattern with increased angiogenesis has been demonstrated recently,[16] which has not yet been shown for a focal infiltration pattern.

Limitations of conventional MRI (without administration of contrast medium) are the incapacity to differentiate between reactive changes like edema or hematoma and residual lesions containing vital tumor cells, and the fact that response of FL in MRI may be delayed. Walker *et al.* found an increasing proportion of patients in MRI-CR

Table 1. Numbers of focal lesions (A) and diffuse infiltration patterns (B) and at first and second MRI.

A

N. of focal lesions	1st MRI (n)	2nd MRI (n)
0	23	23
1-10	35	52
11-20	15	14
> 20	27	11

B

Diffuse infiltration patterns	1st MRI (n)	2nd MRI (n)
Minimal	24	63
Moderate	44	30
Severe	25	2
Salt & pepper	7	5

with ongoing observation after 12, 24, 36 and 48 months, respectively.[8]

In this context, PET-CT seems to allow earlier detection of disease response than MRI. Zamagni *et al.* reported a proportion of 37% and 65% PET negative patients after induction and after ASCT, respectively.[17] Several functional techniques have been established to overcome the disadvantages and to improve the specificity of MRI for the evaluation of changes in bone marrow. Comparison of the findings of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging (DWI) with bone marrow histology have provided further insight into the changes caused by MM.[18,19] These techniques allow at least a semi-quantitative measurement of microcirculation and cellularity, and first results have demonstrated their potential value for treatment monitoring in MM.[20]

However, the discrepancy between IURC and MRI-response implies that MRI provides information on disease activity and tumor mass, not from serological parameters alone. Therefore, a combination of both response classifications helps to improve monitoring of systemic treatment. Further studies should focus on the histological comparison between areas of focal and diffuse infiltration, and clarify the mechanisms leading to the different patterns.

Prognostic significance of MRI findings at first and second MRI

For evaluation of prognostic significance of the number of FL for overall survival a log rank test resulted in *P* values of 0.45 for the first and 0.001 for the second wb-MRI. Kaplan-Meier plots for overall survival according to the number of FL at first and second MRI are shown in Figure 1. In addition, the number of FL at second MRI was of prognostic significance for progression free survival (*P*=0.10 and *P*=0.03 for first and second MRI, respectively). For the previously reported cut off of 0-7 *versus* over 7 FL at first MRI[8] we found a borderline significance for PFS and OAS (*P*=0.06 and *P*=0.04, respectively).

Interestingly, in our study, the number of FL at second MRI showed a significant prognostic effect while that at baseline did not. Hypothetically, the persistence of changes in MRI identifies a subgroup of patients in whom the treatment response of the disease is weaker or may be reflected more slowly in a higher residual tumor mass. Walker *et al.* have been the first to demonstrate that the resolution of lesions in MRI after total therapy are to be associated with a better prognosis,[8] suggesting that residual FL in MRI may represent the source of relapse of the disease. Concerning relapse the following reasons were reported and led to initiation of treatment further on: rise in M-protein in 36 patients (72%), new soft tissue tumor in 5 patients (10%), progressive bone disease in 4 patients

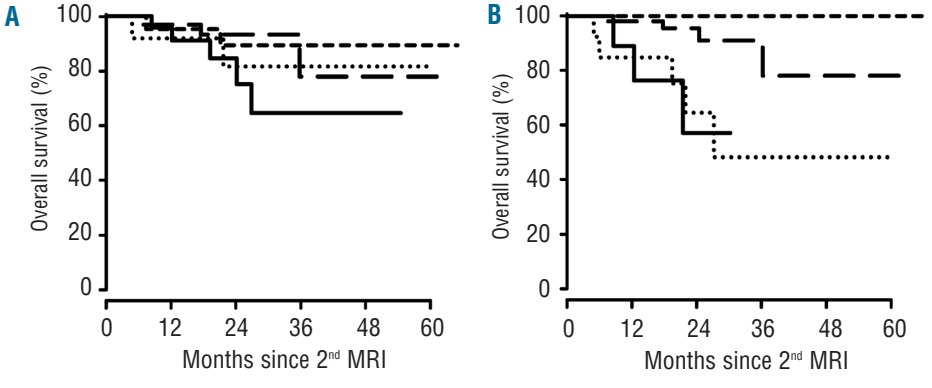
Table 2. Contingency table of treatment response and MRI-derived remission rates, for (A) focal and diffuse (B) response separately.

A

Focal	MRI-CR (n)	MRI-PR (n)	MRI-SD (n)	MRI-PD (n)	Total (n)
seroCR	3	4	3	1	11
seroPR	19	18	23	14	74
seroSD	0	1	2	4	7
seroPD	1	1	0	6	8
Total	23	24	28	25	100

B

Diffuse	MRI-CR (n)	MRI-PR (n)	MRI-SD (n)	MRI-PD (n)	Total (n)
seroCR	9	2	0	0	11
seroPR	49	7	17	1	74
seroSD	3	2	2	0	7
seroPD	2	2	2	2	8
Total	63	13	21	3	100



Line	N. of focal lesions	1st MRI			2nd MRI		
		N. of patients	OS at 2 years	*P*	N. of patients	OS at 2 years	*P*
– – –	0	23	89%	0.45	23	100%	0.001
— –	1-10	35	93%		52	91%	
·····	11-20	15	81%		14	64%	
———	>20	27	75%		11	57%	

Figure 1. Impact of focal lesions at (A) first and (B) second MRI on overall survival (OS).

(8%), decrease in hemoglobin levels in 2 patients (4%) and variegated reasons in 3 patients (meningeosis, hyposecretory progression, increasing pain). Zamagni *et al.* demonstrated that PET-CT derived parameters are sensitive to treatment response and that they have prognostic significance both at first diagnosis and after ASCT.[17] However, there are still not enough PET-CT scanners available and the examination is very expensive because tracers have to be manufactured for each patient. Furthermore, especially if multiple follow-up examinations are necessary, the irradiation dose becomes an issue. Compared to that, MRI scanners, even with the option of whole body imaging, are becoming more and more available with the additional advantages of not needing irradiation or a contrast medium. The sensitivity and specificity of both techniques to detect FL of myeloma in the bone marrow is comparable with a slight benefit for MRI in previous studies.[21,22] In addition, MRI can reliably detect diffuse infiltration. Residual lesions after therapy detected by either technique may be the source of relapse and should, therefore, be taken into account if the decision for further therapy has to be made. To further investigate which imaging method should be used in different clinical settings, both will have to be subject to studies in which a direct analysis is made between them.

In summary, wb-MRI is a valuable, non-invasive tool to monitor treatment of patients with MM and to measure residual disease. It adds important information to the standard IURC defined response assessment. Further developments, such as DCE-MRI and DWI sequences, will lead to a higher sensitivity and specificity, and may add to the findings of established methods.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.
2. Moulopoulos LA, Gika D, Anagnostopoulos A, Delasalle K, Weber D, Alexanian R, et al. Prognostic significance of magnetic resonance imaging of bone marrow in previously untreated patients with multiple myeloma. Ann Oncol. 2005;16(11):1824-8.
3. Lecouvet FE, Vande Berg BC, Michaux L, Jamart J, Maldague BE, Malghem J. Development of vertebral fractures in patients with multiple myeloma: does MRI enable recognition of vertebrae that will collapse? J Comput Assist Tomogr. 1998;22(3):430-6.
4. Kusumoto S, Jinnai I, Itoh K, Kawai N, Sakata T, Matsuda A, et al. Magnetic resonance imaging patterns in patients with multiple myeloma. Br J Haematol. 1997;99(3):649-55.
5. Bauerle T, Hillengass J, Fechtner K, Zechmann CM, Grenacher L, Moehler TM, et al. Multiple myeloma and monoclonal gammopathy of undetermined significance: importance of whole-body versus spinal MR imaging. Radiology. 2009;252(2):477-85.
6. Baur-Melnyk A, Buhmann S, Becker C, Schoenberg SO, Lang N, Bartl R, et al. Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. AJR Am J Roentgenol. 2008;190(4):1097-104.
7. Ghanem N, Lohrmann C, Engelhardt M, Pache G, Uhl M, Saueressig U, et al. Whole-body MRI in the detection of bone marrow infiltration in patients with plasma cell neoplasms in comparison to the radiological skeletal survey. Eur Radiol. 2006;16(5):1005-14.
8. Walker R, Barlogie B, Haessler J, Tricot G, Anaissie E, Shaughnessy JD Jr, et al. Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. J Clin Oncol. 2007;25(9):1121-8.
9. Hillengass J, Fechtner K, Weber MA, Bauerle T, Ayyaz S, Heiss C, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol. 2010;28(9):1606-10.
10. Lecouvet FE, Vande Berg BC, Michaux L, Malghem J, Maldague BE, Jamart J, et al. Stage III multiple myeloma: clinical and prognostic value of spinal bone marrow MR imaging. Radiology. 1998;209(3):653-60.
11. Mariette X, Zagdanski AM, Guermazi A, Bergot C, Arnould A, Frija J, et al. Prognostic value of vertebral lesions detected by magnetic resonance imaging in patients with stage I multiple myeloma. Br J Haematol. 1999;104(4):723-9.
12. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940-8.
13. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San MJ, Chanan-Khan A, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011;117(18):4701-5.
14. Gleeson TG, Moriarty J, Shortt CP, Gleeson JP, Fitzpatrick P, Byrne B, et al. Accuracy of whole-body low-dose multidetector CT (WBLDCT) versus skeletal survey in the detection of myelomatous lesions, and correlation of disease distribution with whole-body MRI (WBMRI). Skeletal Radiol. 2009;38(3):225-36.
15. Barlogie B, Anaissie E, van Rhee F, Pineda-Roman M, Zangari M, Shaughnessy J, et al. The Arkansas approach to therapy of patients with multiple myeloma. Best Pract Res Clin Haematol. 2007;20(4):761-81.
16. Moulopoulos LA, Dimopoulos MA, Christoulas D, Kastritis E, Anagnostou D, Koureas A, et al. Diffuse MRI marrow pattern correlates with increased angiogenesis, advanced disease features and poor prognosis in newly diagnosed myeloma treated with novel agents. Leukemia. 2010;24(6):1206-12.
17. Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood. 2011;118(23):5989-95.
18. Nosas-Garcia S, Moehler T, Wasser K, Kiessling F, Bartl R, Zuna I, et al. Dynamic contrast-enhanced MRI for assessing the disease activity of multiple myeloma: a comparative study with histology and clinical markers. J Magn Reson Imaging. 2005;22(1):154-62.
19. Hillengass J, Bauerle T, Bartl R, Andrulis M, McClanahan F, Laun FB, et al. Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone marrow infiltration in patients with monoclonal plasma cell disease: a comparative study with histology. Br J Haematol. 2011;153(6):721-8.
20. Lin C, Luciani A, Belhadj K, Deux JF, Kuhnowski F, Maatouk M, et al. Multiple myeloma treatment response assessment with whole-body dynamic contrast-enhanced MR imaging. Radiology. 2010;254(2):521-31.
21. Shortt CP, Gleeson TG, Breen KA, McHugh J, O'Connell MJ, O'Gorman PJ, et al. Whole-Body MRI versus PET in assessment of multiple myeloma disease activity. AJR Am J Roentgenol. 2009;192(4):980-6.
22. Zamagni E, Nanni C, Patriarca F, Englaro E, Castellucci P, Geatti O, et al. A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica. 2007;92(1):50-5.