Research Article

The probably use of MR-spectroscopy and diffusion weighted-MRI of bone marrow for treatment monitoring in patients with chronic lymphatic leukemia

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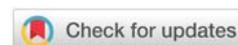[3]Department of Haematology, University Hospital Quironsalud Madrid, Spain

Abstract

Objectives: To assess the usefulness of proton MR-spectroscopy (1H-MRS) and diffusion-weighted MRI (DW-MRI) sequences in the follow-up of CLL-patients with chemotherapy treatment. The monitoring of CLL-patients susceptible to chemotherapy treatment is complicated due to the difficulty in assessing the response to treatment. Chemotherapy leads to changes in bone marrow composition and these changes can be evaluated by functional MR-sequences.

Methods: 23 patients diagnosed with CLL by our hospital's Hematology Service underwent a lumbar MR prior and post-chemotherapy applying 1H-MRS and DW-MRI. The concentrations of water and lipids were quantified applying the quantification program LCModel. The Apparent Diffusion Coefficient (ADC) values were calculated with the Functool program (GE). The Wilcoxon sign test was used to compare pre and post treatment results, considering statistically significant P values lower than 0.05.

Results: Responder patients decreased the ratio H_2O/lipids concentration measured with 1H-MRS and increased the ADC value on DW-MRI in post-treatment studies ($P<0.05$). Patients without response increased the ratio and decreased the ADC values or did not modify the data.

Conclusion: 1H-MRS and DW-MRI of spinal bone marrow are non-invasive and repeatable techniques that might help in follow-up monitoring of patients with CLL.

Introduction

In recent years it has become a useful practice in certain oncohematological pathologies, such as multiple myeloma, applying dedicated techniques as diffusion weighted MRI (DW-MRI) to diagnose and monitor patients [1-3] However, this technique and especially, proton spectroscopy-MR (1H-MRS) are not commonly used in the monitoring of patients with CLL, with scarce reports in the literature [4-6].

The disease has a very heterogeneous clinical course, with patients living decades without treatment and others with rapidly fatal evolution. The follow-up of patients under treatment sometimes raises doubts about the response, since

clinical and analytical data are very variable, requiring a very close and long-term follow-up to define a conclusive response. Bone marrow biopsy is only used for diagnosis, not for follow-up, except in patients included in clinical trials.

The treatment causes changes in the cellularity of the bone marrow and, therefore, changes in the metabolic composition, affecting the proportion of H_2O and lipids, which can be evaluated and quantified with either DW-MRI and 1H-MRS, which are safe and can be repeated when necessary.

In normal adult bone marrow, the main component is fat, with poor metabolic representation of H_2O with a ratio in favor of lipid concentration [7]; when there is leukemic infiltration, adipocytes are replaced by leukemic cells, rich in aqueous content, switching the ratio. On the other hand, a decrease value of the Apparent Diffusion Coefficient (ADC) is generally noted in an infiltrated tumoral tissue [8,9]. The infiltrated bone marrow will show changes in diffusion, as the tumor cell volume increases.

The objective of the study is to analyze whether an increased fat-water ratio in spectra and increased ADC in DW-MRI could be associated with response to chemotherapy treatment in patients with CLL, aiding haematologist in the patient monitoring in the daily clinical practice.

Material and methods

Patients

Twenty-three patients diagnosed with CLL by our hospital's Hematology Service were included in the study. All patients required chemotherapy based on the criteria established by the International Workshop On CLL (IwCLL2008): progressive medullary insufficiency defined by anemia or thrombocytopenia, progressive splenomegaly, growth of large adenopathic conglomerates, lymphocyte duplication time of 6 months or less, or lymphocytosis increase of more than 50% in 2 months, anemia and/or autoimmune thrombocytopenia that do not respond to immunosuppressive treatment and general symptoms.

The exclusion criteria were bone, hematological or concomitant pulmonary diseases, oncological treatments other than those inherent to their basal pathology, or patients who could not undergo an MRI study (pacemaker, pelvic or lumbar surgical material).

All patients signed informed consent and the study was approved by the hospital ethics committee.

The treatment used was chemo-immunotherapy FCR (Fludarabine-Cyclophosphamide-Rituximab), BR (bendamustine-rituximab) or CHOP-R (cyclophosphamide-adriamycin-vincristine-methylprednisolone-rituximab) and new treatments such as ibrutinib and lenalidomide.

After two months of chemotherapy treatment, the degree of response was measured in all patients. The patients were classified as responders or non-responders in the

hematological department based on peripheral blood tests normalization (hemoglobin values, platelets and lymphocytes), morphological response of thoracic and abdominopelvic CT (lymphadenopathies, splenomegaly or soft tissue masses). Indeed, direct measurement with post-treatment bone marrow aspiration/ biopsy was also performed in these patients.

Three patients did not complete the study and one patient died during the treatment; therefore, complete data were finally obtained from 19 patients.

Image studies

All patients underwent a lumbar MRI study prior to chemotherapy treatment focused on the L3 vertebra with a routine T1-weighted morphological sequences to which a 1H-MRS and a DW-MRI study was added. The study does not require intravenous contrast and has a duration of 30 minutes.

A multichannel column coil was used, with spectral acquisitions in 3T magnet (Signa HDx, GEHealthcare, Milwaukee, WI, USA). The basal morphological image is a sagittal T1 (TE:min;TR:500ms, bandwidth 62.2 kHz; FOV 22 cm; thickness 5 mm; spacing 1 mm).

The DW-MRI was acquired in axial plane, with parallel imaging (ASSET) with the following parameters: factor b of 0 and 900 mm²/s, fat suppression, matrix of 128 x 128 and 8 NEX; FOV 20, TR >8000 ms; TE minimum 75-90 ms; cutting thickness: 5 mm; gap 1mm. Acquisition time was 3'30''.

The spectral technique used is the PRESS technique (Point Resolved Spectroscopy) and the parameters used are TE 37 ms, TR 3000 ms, 64 averages without H_2O suppression, sweep width=5000 Hz, autoshimming. The voxel used has dimensions of 15×15×20mm and is located in the center of the lumbar vertebra L3. Four to six saturation bands are used to increase homogeneity and avoid elements of confusion (Figure 1). The steam sequence (STEAM) shows advantages compared to PRESS sequence for fat quantification [10,11], but the acquisition is more complex for a daily routine practice.

The radiological data we collected from each patient pre- and two months post-treatment were: signal intensity on T1-weighted sequences (IT1), mean value of apparent
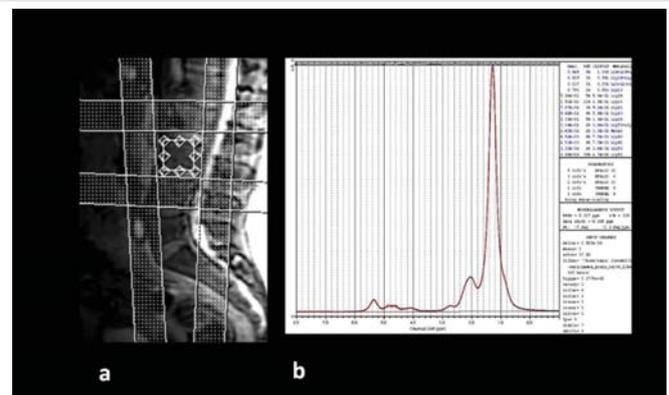

Figure 1: MR-spectral curve acquisition technique in L3.

diffusion coefficient (ADCm in mm² /seg) and the ratio of the concentration (CC) of H_2O / lipid metabolites (H_2O/Lip CC).

The lipids are located at 1.6-0.8 ppm in the spectral curve and are mainly from the methyl (CH3) and methylene (CH2) groups. The H_2O peak is located between 4.7-4.8ppm. Concentrations derived from the raw data obtained from the spectral curves in the MR were processed by the quantification program LCModel (S. Provencher), analyzing the spectra as a linear combination, based on a group of complete models of spectroscopies of metabolites in "in vitro" solution.

The ADCm value is calculated in an independent console, with the Functool program (GE), by means of an ROI that covers the entire area of the vertebral body L3 (Figure 2).

Statistical analysis

The frequencies of the categorical variables were expressed as absolute number and percentage. The Kolmogorov–Smirnov test was used to check whether the continuous variables followed a normal distribution. The median and the Interquartile Range (IQR) were used to describe the quantitative variables. The Wilcoxon sign test was used to compare pre and post treatment results, considering statistically significant P values lower than 0.05. The statistical package SPSS version 21.0 (IBM, Armonk, New York, USA) was used for data analysis.

Results

A total of 13 males and six females between the ages of 55 and 76 were studied. The clinical and analytical data collected from the patients are provided in the supplementary Table 1.

Of the 19 patients, 15 were responders and four patients were non-responders (had no analytical or morphological response in CT, or the bone marrow biopsy was positive).

Quantitative metabolite data obtained from spectra and mean ADC values of recruited patients pre- and post-treatment are provided as supplementary data (supplementary Tables 2,3).

Pre- and post-treatment results were analyzed in both the non-responder group (Table 1) and the responder group (Table 2). Patients with response, increased the signal intensity in bone marrow signal on T1-weighted sequences and the corresponding IT1 values ($P<0.009$). The post-treatment spectra in responder patients evidence significant reduced values in the H_2O /lipid CC ($P <0.002$) (Figure 3); patients without response either increased the value or did not modify it (Figure 4). Responders patients increased ADCm values ($P <0.006$).

Discussion

The follow-up of patients with CLL susceptible to chemotherapy treatment (those with active disease and adverse prognostic factors) is complicated due to the difficulty in assessing the response to treatment, the frequent absence of clinical symptomatology, and the fact that conventional imaging studies used for follow-up such as CT take longer to
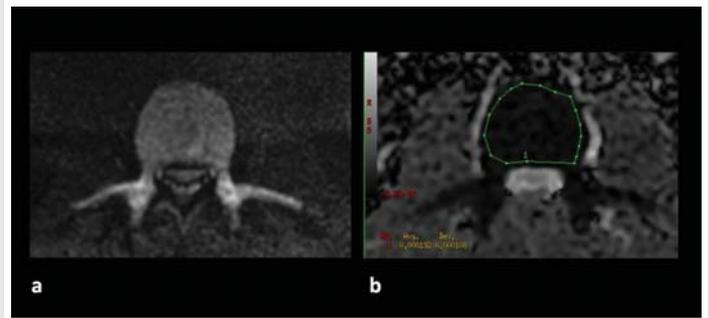

Figure 2: Diffusion image and ADC map in patient with CLL. Typical hypersignal of infiltration in the diffusion image (A), with a very low mean ADC value (0.192x10-3 mm2 / sec) (B).

**Table 1:** Pre and post-treatment comparison in non-responder patients (n=4).

	Pre-treatment median (IQR)	Post-treatment median (IQR)	*P*
I T1	149.4 (96.4-310.2)	199 (86.5-326.7)	0.715
ADCm (mm ²/ seg)	0.381 (0.346-0.423)	0,452 (0.437-0.877)	0.068
H_2O /lipid CC	0.311 (0.059-12.671)	0.283 (0.0455-0.14)	0.164

Table 2: Pre and post-treatment comparison in responder patients (n=15).

	Pre-treatment median (IQR)	Post-treatment median (IQR)	P
I T1	261.8 (214.2-348.3)	410.2 (303.8-484.7)	0.009
ADCm (mm ²/ seg)	0.413 (0.343-0.51)	0.577 (0.469-0.656)	0.006
H_2O /lipid CC	0.109 (0.052-0.386)	0.037 (0.023-0.047)	0.002
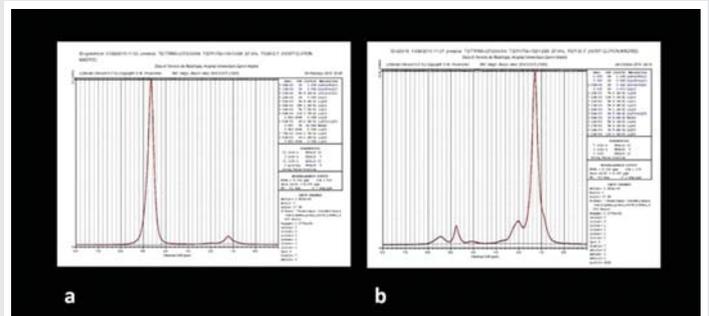
Figure 3: Graphic example of changes in the spectra in a patient with good clinical-radiological response. (a) Pretreatment spectra. (b) After treatment an evident inversion of H2O (4.7 ppm) (arrow) and Lipid (1.6-0.8ppm) (open arrow) peaks, is seen.
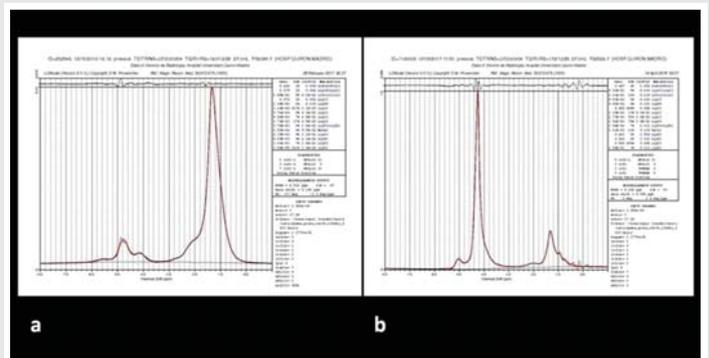
Figure 4: Graphic example of changes in the spectra in a patient with worsening during treatment. Increase of H2O peak (4.7 ppm) and decreased of the lipids peak (1.6-0.8ppm).

show changes than would be desirable. The need, on occasions, to confirm the response with the histological medullary study may delay treatments and involves invasive tests for the patient, hence the initiative to conduct this study with the aim of improving the monitoring of these patients with safe and repeatable techniques.

1H-MRS and DW-MRI sequences may identify treatment changes in the bone marrow, prior to morphological changes, even after a few weeks of chemotherapy treatment, allowing safe early monitoring of the treatment and avoiding unnecessary biopsies.

Although this is a pilot study and the sample size is limited, the found differences could indicate that 1H-MRS and DW-MRI of spinal bone marrow are non-invasive and repeatable techniques that might help in follow-up monitoring of patients with CLL.

1H-MRS adds metabolic tissue information, complementary to the structural information from the conventional MR studies. This technique provides a noninvasive means of assessing in vivo bone marrow metabolites that can shed light on cellular concentrations and therapeutic response. 1H-MRS easily can be added to routine lumbar MR with little time and cost penalty, with patients screened simultaneously.

In normal adult bone marrow, the main component is fat, with hyper-signal in the vertebral bodies on T1-weighted sequences. When there is leukemic infiltration, the aqueous content of the bone marrow is higher, decreasing the T1 signal intensity of the bone marrow [12-17], so conventional MRI sequences can sometimes be helpful.

The results of this study show significant differences in signal intensity on T1-weighted sequences, ADCm and H_2O/Lip CC obtained before and after treatment in patients who responded to chemotherapy, while no significant differences were found in non-responders.

In our pilot study, a significant increase in signal on T1-weighted sequences was observed, (P=0.009), in patients who respond positively to chemotherapy treatment complementing the hematology service's evaluation of the response.

The limitation occurs when there is a lower than expected conversion of fat marrow after treatment, and therefore the signal strength value is not modified excessively. This occurs in patients with "packed" infiltration pattern where the fibrosis component predominates over fat replacement and therefore the hyper-signal in T1 sequences is lower. Indeed, a seroconversion phenomenon may also occur with an increase in healthy hematopoiesis, with a higher proportion of H_2O, which will also not increase the T1 signal.

In the adult axial skeleton, when it is spectrally evaluated, two major spectral peaks can be found: that of lipids and that of H_2O [18-23], with a ratio in favor of lipid concentration. In this regard, a leukemic infiltration would cause changes in the spectral curve, with an increase in the concentration of the H_2O peak.

In our pilot study, it is possible to analyze the individual variation of concentrations of pre and post-treatment spectral metabolites, especially the variation of the post-treatment H_2O/lipid CC. A priori, the data obtained from these analyses would confirm our working hypothesis and are in concordance with previous studies [5,6,23,24].

The most statistically significant results are the clear decrease in the H_2O/lipid CC in all the responder patients.

In patients with positive response to treatment, the H_2O/lipid ratio decreased (p<0.002), indirectly indicating a reduction in leukemia cells rich in H_2O and an increase in the bone marrow adipocytes. In one patient with a partial (not complete) response to treatment, no significant reduction in the H_2O/lipid ratio was observed, and there was even a slight increase in the H_2O/Lip CC. Perhaps this fact can be explained by a phenomenon of hypercellular haematopoietic bone marrow reconversion (see below in the "study limitations" section), with an H_2O content exceeding that of fat bone marrow; in this patient the partial positive response (based on the peripheral blood data) was achieved by the increase of the absolute lipid concentration and of the IT1 value.

In the four patients without response to chemotherapy treatment, absolute lipid concentrations remained low and the H_2O/lipid CC did not vary statistically significant.

Changes in ADC values are widely described in the literature on musculoskeletal oncology pathology [7,8,25-30]. DW studies reveal a decrease value of the ADC in the infiltrated tumoral tissue, changing as the tumor cell volume increases.

Regarding the data obtained from the pre and post-treatment diffusion maps in our study, a statistically significant increase in the ADC value (P <0.006) was observed in all responder patients.

Diffusion as a direct marker of cellularity was clearly diminished in bone marrow with greater cellular infiltration; the drop of the ADC values was higher in the leukemic infiltrations forms called "packed patterns" of medullary biopsies, with a great level of fibrosis that does not allow the diffusion of H_2O protons in the extracellular space.

In the four patients with no response, the ADC values did not show significant changes Finally, it should be noted that both techniques are harmless for the patient, with a total duration of less than 30 minutes. Both techniques are reproducible and validated in the literature, and in view of the results they could be very useful in monitoring treatment.

Study limitations

One of the limitations of the study was the acquisition of overall spectral image. It is well known that STEAM spectral sequences are better than PRESS for fat quantification in bone marrow, but we did not take into consideration absolute water or lipid values. Indeed, the comparison between the pre and post chemotherapy treatment H_2O/lipid ratio was made patient by patient. Other major advantages for PRESS acquisition are

that technicians are more comfortable in their daily practice with this technique.

In three of the patients evaluated, who presented a massive interstitial-packed leukemic infiltration (>90%) in the bone marrow biopsy and large fibrosis component, the suppression of H_2O in the spectral acquisition was practically impossible, being this fact necessary for field homogeneity and for avoiding long acquisition times. Furthermore, it is known that resonance fibrosis presents low signal intensity on T1 weighted sequences, causing a low signal-to-noise ratio in MRI, especially in 3T magnets, where the studies were performed. Therefore, we decided to conduct the studies with a 1.5 Tesla magnet, less influenced by magnetic susceptibility and requiring less field homogeneity for spectral acquisition, thus allowing us to obtain the data.

Another limitation of the study is the phenomenon of medullary hyperplasia, which makes it difficult to interpret the results after chemotherapy treatment. It is a well-known phenomenon in oncological studies of lymphoma treatment monitoring with PET-FDG, where diffuse medullary hypermetabolism with marked glucose uptake is reflected, and in evaluation studies with spectroscopy of granulocytic colony stimulation factors in oncological or deposit diseases [31-35]. There is an increase in cellularity, generally from a cellular series, the myeloid, which metabolically translates into an increase in the H_2O component of the cells, which may be a factor of confusion in the spectral curve. Fortunately, it is not usually correlated with the analytical response; nor is it accompanied by a significant decrease in lipid concentration or a decrease in pre-treatment ADC values.

Conclusion

Although a larger sample of patients will be required for validation, our results show that these radiological tools could make it easier for hematologists to monitor treatment and perhaps in the future use the data as complementary predictive factors of therapy response.

Acknowledgement

We wish to thank Peter Bonney for his support in proofreading this article.

Novelty statements

1. The combined use of the bone marrow MR-spectroscopy and diffusion in the evaluation of treatment of CLL patients.

2. The early decrease of the ratio H2O/ lipids and the increase of the apparent diffusion coefficient, in patients with good response to treatment.

3. The probably use in daily practice of these functional techniques in the follow up of CLL patients.

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