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Brain glucose metabolism in patients with newly diagnosed multiple myeloma significantly decreases after high-dose chemotherapy followed by autologous stem cell transplantation

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Abstract

Purpose: The aim of this study was to compare the effect of intensive therapy (consisting of high-dose chemotherapy followed by ASCT (HDC/ASCT)) and conventional standard-dose chemotherapy (CDC) on brain $^{18}$FDG uptake, as an indicator of glucose metabolism, in multiple myeloma (MM) patients.

Materials and Methods: Twenty-four patients with newly diagnosed MM were included. Sixteen patients received HDC/ASCT, including bortezomib-based induction therapy, and eight patients received CDC. $^{18}$FDG-PET/CT was performed 1 hour (1h) and 3 hours (3h) following tracer administration before and after the treatment. The manual segmentation of supratentorial and cerebellum of each patient was performed by two independent observers. The data was expressed as global mean standardized uptake values (GSUVmean). Wilcoxon signed-rank test was used to compare changes from before to after treatment.

Results: A significant decrease in the GSUVmean of supratentorial brain and cerebellum was observed after treatment in the patients who received HDC/ASCT (1h scans: 7.03± 1.18 vs. 6.56± 0.94; p= 0.03 and 7.01± 1.08 vs. 6.34± 0.93; p= 0.01, respectively). GSUVmean changes in the patients who received CDC were not significantly different after treatment (1h scans: 6.47± 1.16 vs. 6.21± 0.91; p= 0.40 and 6.30± 1.21 vs. 6.09± 0.86; p= 0.62, respectively). The same findings were observed for 3h scans. A high level of agreement was observed between two operators.

Conclusion: MM patients who received HDC/ASC demonstrated a significant decrease in $^{18}$FDG uptake in the supratentorial brain and cerebellum, while patients who received CDC did not demonstrate significant changes in the brain $^{18}$FDG uptake.

Keywords: Positron Emission Tomography; $^{18}$F-FDG; Multiple Myeloma; Chemotherapy; Chemo-Brain; High-Dose Treatment
Introduction

Literature suggests that nearly all frequently used chemotherapeutic drugs can cause adverse neurological effects [1-3], and patients with systemic chemotherapy often experience cancer-related cognitive impairment (CRCI) such as cognitive impairment, memory, and concentration deficits [4,5]. There have been studies suggesting that chemotherapy, especially high-dose chemotherapy, causes changes in brain structure such as a reduction in regional brain volume, atrophy of cerebral gray matter, and demyelination of white matter [6-9]. In addition to chemotherapy, neurocognitive dysfunction is a serious cause of morbidity in hematopoietic cell transplant recipients, yet little is known about it [10,11]. Up to now, investigations of CRCI (also referred to as chemo-brain) have been limited to studies that employ clinical neuropsychological methods that were initially designed to detect focal lesions [12].

$^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) has shown to be a powerful tool for analyzing changes in brain function in a wide range of neurological and psychiatric disorders. Molecular imaging with $^{18}$FDG-PET has been shown to detect early changes in cerebral glucose metabolism before structural abnormalities become apparent, as compared to MRI and CT scans, which demonstrate brain atrophy usually after significant disease progression [13]. In regard to molecular imaging, chemo-brain has been suggested to be associated with a decrease in cerebral glucose metabolism [14] and therefore, can be measured with $^{18}$FDG-PET. However, there is a dearth in the literature that compares the effects of high-dose therapy and conventional-dose therapy on brain $^{18}$FDG uptake.

In this study, we aimed to compare the effects of intense therapy (consisting of high dose chemotherapy followed by autologous stem cell transplantation (HDC/ASCT)) and conventional standard-dose chemotherapy (CDC) on whole-brain glucose metabolism of MM patients. To achieve this purpose, we
used a global $^{18}$FDG-PET quantification, which offers an assessment of changes in $^{18}$FDG metabolism for the entire brain. The validity of this methodology was already tested in a previous study by Pourhassan Shamchi et al. [15]. To assess the degree of reproducibility, two different operators conducted the analysis. Since a previous study has shown the patients who received high-dose therapy had a higher risk of cognitive impairment compared to the patients that received CDC [16], we hypothesized that HDC/ASCT would cause a more significant decrease in $^{18}$FDG brain uptake after treatment than CDC in MM patients.

Methods and Materials

Subjects

This study was performed as a part of Functional Imaging in MM patients (FULIMA study). FULIMA is a prospective study approved by the Danish National Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT02187731), and conducted in accordance with the Declaration of Helsinki. The project was a two-center study at Departments of Hematology, Odense University Hospital, and Vejle Hospital, Denmark. The study comprised of patients who were referred with a suspicion of having treatment-demanding MM. Inclusion criteria were subjects age >50 years, suspected treatment-demanding MM in concordance with Danish cancer society criteria, and signed the consent form. Exclusion criteria were history of treated MM, current or recent radiotherapy or surgery less than two weeks prior to screening, history of prior malignancy, with at least three years disease-free period, known inflammatory disease or severe medical or psychiatric conditions, pregnancy or breastfeeding, POEMS syndrome (plasma cell dyscrasia with poly-neuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes).
Forty-two participants with MM were included in the FULIMA project. Two nuclear medicine physicians evaluated the quality of brain $^{18}$FDG PET/CT scans at the University of Pennsylvania and Odense Hospital. Eighteen patients were excluded due to poor quality of brain $^{18}$FDG-PET/CT scans or lack of either baseline or end of treatment scans. Finally, twenty-four patients with MM (20 males and four females, mean age = 64.3 ± 8.5), who had $^{18}$FDG scans before and after treatment and high-quality brain PET, were included in this study. Thirteen males and three females (mean age= 60.6 ± 6.3) received HDC/ASCT, and seven males and one female (mean age= 71.8 ± 7.6) received CDC (Table 1). The patients received standard first-line treatment, including bortezomib-based induction therapy followed by cyclophosphamide 2000mg/m$^2$ and melphalan 200mg/m$^2$ before infusion of stem cells for the HDC/ASCT group (Appendix 1).

PET/CT

PET/CT examination was performed in accordance with the European Association of Nuclear Medicine (EANM) guidelines [17], including quality control of PET/CT scanners and validation of SUV measurements according to the same guidelines. After a minimum of 6 hours of fasting and a confirmed blood glucose concentration of below 8mmol/L (5.52 ± 0.41), the patients received an intravenous injection of approximately 4MBq/kg $^{18}$FDG. All underwent whole-body $^{18}$FDG-PET/CT scans at 1 hour (h) (69.29 ± 10.34) and 3h (182.63 ± 4.89) following administration of tracer. Between the two time-points, the patients were kept fasted in the waiting area and instructed to rest. All patients underwent dual time point (DTP) $^{18}$FDG-PET/CT at time of diagnosis (baseline) and eight weeks and two weeks after completion of treatment for the HDC/ASCT group and CDC group, respectively. $^{18}$FDG-PET/CT scans were performed using GE STE/VCT/Rx/690PET/CT (GE, Milwaukee, WI) or Philips Gemini TF (Philips, Amsterdam, Netherlands). Low-dose CT (LDCT) scan was performed (120 kV, 30-110 mA Smart mA, collimation 16/64*0.625, rotation time 0.5sec, pitch 0.984, slice thickness 3.750mm) and followed by a 3-D PET scan using a whole-body acquisition protocol from vertex to below the knee.
Trans-axial reconstruction was performed (standard filter, slice thickness 3.750, increment 3.270). Acquisition times were 2.5 min/field of view (FOV) for the 1h scan and 3.5 min/FOV for the 3h scan. The LDCT scan was used for attenuation correction. PET images were reconstructed with iterative algorithms (Ordered Subset Expectation Maximization (OSEM), (four iterations, 24 subsets). The patients underwent imaging on the same scanner at baseline and after the end of treatment.

Quantitative analyses

Using OsiriX software (Pixmeo SARL, Bernex, Switzerland), $^{18}$FDG uptake in the supratentorial brain, and the cerebellum was measured for both scans (1h and 3h). Regions of interest (ROIs) were manually drawn of the supratentorial and infratentorial brain based on the following criteria for each (Fig. 1).

Tentorium cerebelli is the extension of the dura mater, which separates the supratentorial region of the brain from cerebellum. The supratentorial brain is the area located above the tentorium cerebelli, and cerebellum is the area located beneath it. The regional cerebral metabolic activity was determined by multiplying the regional cerebral volume and SUVmean from each slice. The global SUVmean (GSUVmean) was calculated by dividing the global cerebral metabolic activity by the total cerebral volume (Fig. 1). The validity of this method of quantification has already been established and tested in another study [15]. The percentage of change for each patient between pre-treatment and post-treatment was calculated. Three scans highlight the change in brain glucose metabolism pre and post treatment (Fig. 2). To assess the degree of agreement, two different operators conducted the analysis.

Statistical analysis
Statistical analysis was performed using SPSS Statistics version 25 (IBM Corp, NY, USA). Student t-test and chi-square were used to compare the two groups' characteristics. Wilcoxon signed-rank test (non-parametric, small sample) was used to compare changes between pre-treatment and post-treatment. Intraclass correlation analysis was used to assess interrater reliability. Statistical significance was defined by a p-value less than 0.05.

Results

In the patients who received high-dose therapy (HDT group), a decrease in the GSUVmean of supratentorial and cerebellum was observed in 1h scans from pre-treatment to post-treatment (from 7.03 ± 1.18 to 6.56 ± 0.94; p = 0.03 and from 7.01 ± 1.08 to 6.34 ± 0.93; p = 0.01, respectively) (Table 2). The same findings were present for 3h scans (from 7.25 ± 1.33 to 6.78 ± 1.10; p = 0.04 and from 6.52 ± 1.02 to 5.99± 0.59; p= 0.01, respectively). The changes in supratentorial and cerebellum 18FDG uptake in the patients who received CDC were not significant (1h scans: 6.47± 1.16 vs. 6.21± 0.91; p= 0.40 and 6.30± 1.21 vs. 6.09± 0.86; p= 0.62, respectively) (Table 2) (Figure 2). High level of agreement was found between two operators (pre-treatment supratentorial 1 hour ICC: 0.952, 95% CI: 0.893-0.984, pre-treatment cerebellum 1 hour ICC: 0.964, 95% CI: 0.927-0.992, post-treatment supratentorial 3 hours ICC: 0.943, 95% CI: 0.861-0.976, post-treatment cerebellum 3 hours ICC: 0.957, 95% CI: 0.912-0.989) (Table 3).

Discussion
In this study, we used a global quantification methodology to compare the effects of intensive therapy (consisting of HDC/ASCT) and CDC on $^{18}$FDG uptake in the supratentorial and cerebellum areas of the brain in MM patients. We observed a decrease of $^{18}$FDG uptake in supratentorial and cerebellum areas in both groups. Various studies have shown a decrease in brain metabolism in patients treated with chemotherapy. A study incorporating 10 patients with non-small-cell lung cancer [18] showed a significant decline in $^{18}$FDG brain metabolism after chemotherapy, involving both the gray matter structures and the white matter network such as the subcortical structures and corpus callosum. Another study [14] using $^{18}$FDG-PET and $[\text{O-15}]\text{H}_2\text{O}$ emphasized the long-term chronic neurotoxicity after chemotherapy (treated more than five years beforehand) in patients with breast cancer. However, we only found a statistically significant decrease of $^{18}$FDG after treatment in patients who received intensive therapy, consisting of HDC followed by ASCT. This result is comparable to a prior study by Van Dam et al. that found that the patients who received high-dose therapy had 8.2 times higher risk of cognitive impairment compared to 3.5 times higher risk for the patients that received standard-dose chemotherapy [16].

Cognitive problems are a significant concern for patients undergoing stem cell transplant. More than 50% of patients who undergo stem cell transplant report cognitive changes and over 25% of patients have cognitive problems rated as moderate to severe [19-21]. A study by Harder et al. investigated the effects of bone marrow transplantation on cognitive functioning in forty patients, 87.5% of whom underwent allogeneic transplantation [22]. They found a Mild to moderate cognitive impairment in 24 patients (60%) [22]. The results of this current study showed that in
addition to high-dose chemotherapy, ASCT could cause a significant decrease in FDG uptake of the brain.

In most of the previous studies for measuring $^{18}$FDG uptake in the brain, researchers utilized regional quantitation methods, where they showed decreased $^{18}$FDG metabolism in the certain subcortical and cortical regions rather than offering a complete assessment of changes in $^{18}$FDG metabolism for the entire brain. However, we think a global approach of $^{18}$FDG brain provides a more comprehensive assessment and, as a result, may predict cognitive decline at an earlier stage [15,23]. Sorokin et al. [23] utilized a single 3D spherical region as a global assessment approach, in non-Hodgkin lymphoma patients and demonstrated a decrease of 16.9% in metabolic activity after chemotherapy. They showed a mean reduction of $1308.86 \pm 394.74$ SUV-cc ($p=0.03$) in the whole-brain cortical glycolysis after standard chemotherapy, which translated to a decrease of $16.9 \pm 5.04\%$ ($p=0.03$) in the measured structures [23]. Though it was only a small-scale pilot study incorporating 21 patients, the results showed that the concept of global glycolysis assessment is worth to be further explored. Another advantage of the newer method of PET quantification, such as global assessment, is that they can address the problem of high variability that conventional methods such as SUVmax suffer from [24,25] and as a result, can improve the clinical effectiveness of PET-based measurement as a semi-quantitative imaging biomarker [26-28]. We found a high level of agreement between two operators for our proposed methodology (Table 3).
Another finding in the current study was comparable findings on both 1h and 3h scans, which implies that both 1h and 3h scans could be used to detect changes in the brain metabolism of glucose after chemotherapy in MM patients.

The long-term neurologic adverse effects of functional changes of resting glucose metabolism also remain unknown because all follow-up $^{18}$FDG-PET scans were performed eight weeks after the treatment for the HDC/ASCT group and two weeks after the treatment for the CDC group. Moreover, cumulative effects cannot be ruled out.

The MM patients that enrolled in this study received first-line treatment, including bortezomib-based induction therapy. A bortezomib-containing regimen followed by high-dose therapy and ASCT is considered the standard of care for frontline therapy in younger patients with newly diagnosed MM [29]. Bortezomib/cyclophosphamide/dexamethasone was shown to be an effective and well-tolerated induction therapy for transplant eligible patients with MM, improving progression-free survival and overall survival in high-risk patients. However, based on our knowledge, no previous studies evaluated the effects of this therapy on cognitive impairment and brain glucose metabolism of MM patients. In one of the studies that was conducted to determine the tolerance and safety of bortezomib in patients with previously untreated brain metastasis, greater demyelination in hippocampus-associated white matter structures on MRI predicted delayed cognitive function within one month of the treatment [30].

The main limitations of this study are the lack of available clinical information because we retrospectively analyzed the data from a prospective study. This included the lack of mini-mental state examination, which often is used to detect chemotherapy-related cognitive dysfunction.
[31], or clinical outcome data. However, the data generated supports the hypotheses underlying this investigation. As we stated before, in regard to molecular imaging, chemo-brain has been associated with a decrease in cerebral glucose metabolism, which was supported by our results. Furthermore, the sample size was small, and therefore, future prospective studies with a larger number of patients are warranted to confirm these results. We also used two different PET scanners to collect the cases, but since we compared the percentage of change from before to after treatment and each patient underwent imaging at the same PET scanner, the results are minimally affected.

Conclusion

In our study, only patients who received high dose therapy (HDC/ASCT) demonstrated a significant decrease in $^{18}$FDG uptake after treatment, which could imply that chemo-brain tends to happen more often with high dose therapy. In addition, our study suggests that a method that utilizes global assessment of the whole brain may be effective in elucidating subtle changes in $^{18}$FDG uptake in the newly diagnosed MM patients after HDC/ASCT. This global quantitative technique may offer clinicians with a single, objective measure of disease burden for patients with varying levels of cognitive impairment.
The project was funded by:

The Region of Southern Denmark, University of Southern Denmark, Odense University Hospital, Harboe Foundation, The A.P. Møller Foundation (Fonden til lægevidenskabens fremme), Aase & Ejnar Danielsen Foundation, The Family Hede Nielsen Foundation.

Conflict of interest disclosure:

Authors declare that they have no relevant conflict of interest.

Author contributions:

All authors have made substantial contributions in the following categories:

1. Patient selection and recruitment, PET image analysis, data analysis.
2. Manuscript drafting, assessment of data reproducibility.
3. Revising the manuscript and proving the final content of manuscript.

Acknowledgements:

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**Table 1.** Patients Characteristics
<table>
<thead>
<tr>
<th></th>
<th>HDC/ASCT</th>
<th>CDC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60.62±6.28</td>
<td>71.75±7.59</td>
<td>.001</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13 Males</td>
<td>7 Males</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>3 Females</td>
<td>1 Females</td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.30± 0.06</td>
<td>1.20± 0.06</td>
<td>0.78</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>7.63± 1.27</td>
<td>6.98± 1.48</td>
<td>0.27</td>
</tr>
<tr>
<td>B2M (mg/L)</td>
<td>245.60±113.21</td>
<td>304.87±136.04</td>
<td>0.27</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38.25± 4.83</td>
<td>35.62± 6.27</td>
<td>0.26</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>225.93± 65.86</td>
<td>233.62± 36.51</td>
<td>0.76</td>
</tr>
<tr>
<td>ISS</td>
<td>ISS1=10</td>
<td>ISS1=4</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>ISS2=4</td>
<td>ISS2=3</td>
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<td>ISS3=1</td>
<td>ISS3=1</td>
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<td></td>
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<tr>
<td>R-ISS</td>
<td>R-ISS1= 5</td>
<td>R-ISS1= 3</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>R-ISS2= 10</td>
<td>R-ISS2= 5</td>
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</tbody>
</table>
Blood glucose (mmol/L) (mean +/-SD)

<p>| | | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Unknown</td>
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<td></td>
</tr>
<tr>
<td>5.48±0.44</td>
<td>5.6±0.36</td>
<td>0.66</td>
</tr>
</tbody>
</table>

HDC/ASCT: High dose chemotherapy/autologous stem cell transplantation; CDC: Conventional-dose chemotherapy; Hgb = Hemoglobin; B2M = Beta2 microglobulin; LDH = Lactate dehydrogenase; ISS = International staging system; R-ISS = Revised international staging system
Table 2. Comparison of global $SUV_{mean}$ changes in the HDC/ASCT and CDC groups at 1 hour and 3 hours scans in supratentorial and cerebellum. Data are presented as mean±SD

<table>
<thead>
<tr>
<th></th>
<th>1 hour</th>
<th></th>
<th>3 hours</th>
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<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
<td>p</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td><strong>HDC/ASCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>7.03± 1.18</td>
<td>6.56± 0.94</td>
<td>0.03</td>
<td>7.25± 1.33</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>7.01± 1.08</td>
<td>6.34± 0.93</td>
<td>0.01</td>
<td>6.52± 1.02</td>
</tr>
<tr>
<td><strong>CDC</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>6.47± 1.16</td>
<td>6.21± 0.91</td>
<td>0.40</td>
<td>7.06± 1.34</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>6.30± 1.21</td>
<td>6.09± 0.86</td>
<td>0.62</td>
<td>6.34± 1.38</td>
</tr>
</tbody>
</table>

HDC/ASCT: High-dose chemotherapy/ autologous stem cell transplantation; CDC: Conventional-dose chemotherapy
Table 3. Intraclass correlation coefficient (ICC) for assessment of interobserver reliability

<table>
<thead>
<tr>
<th></th>
<th>ICC</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Pre-treatment supratentorial 1 hour</td>
<td>0.952</td>
<td>0.893-0.984</td>
</tr>
<tr>
<td>Pre-treatment cerebellum 1 hour</td>
<td>0.964</td>
<td>0.927-0.992</td>
</tr>
<tr>
<td>Post-treatment supratentorial 3 hours</td>
<td>0.943</td>
<td>0.861-0.976</td>
</tr>
<tr>
<td>Post-treatment cerebellum 3 hours</td>
<td>0.957</td>
<td>0.912-0.989</td>
</tr>
</tbody>
</table>
Figure 1. Placement of ROIs using Osirix for supratentorial and cerebellum areas. Tentorium cerebelli was used to separate supratentorial region of the brain from cerebellum.
Figure 2. Comparison of global $^{18}$FDG uptake alteration after chemotherapy on pre-treatment and post-treatment FDG PET scans. Patients A and B received HDC/ASCT in contrast to patient C, who only received CDC. Patients A and B had a higher reduction in global $^{18}$FDG uptake compared to patient C.
References:


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**Supplemental Data File (.doc, .tif, pdf, etc.)**

*Appendix- chemobrain- treatment.docx*