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Prediction of therapeutic outcomes and toxicities with high-dose Methotrexate–based chemotherapy for elderly patients with primary central nervous system lymphoma – Comparative study between elderly patients aged over 80 and under 80 –

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Abstract

High-dose methotrexate (HDMTX) chemotherapy has improved survival for patients with primary central nervous system lymphoma (PCNSL). It is unclear if late-stage (aged over 80) elderly patients should be treated the same as early elderly (aged less than 80). This study focused the response and adverse effects of HDMTX in patients aged over 60, comparing those over 80 (Group A) and 60-80 (Group B).

Patients were separated based on pretreatment scores (based on Karnofsky performance scale, renal function and hematopoietic potential). The frequency of severe side effects and overall survival were compared between the two groups and three pretreatment categories. Three patients in Group A and four in Group B had severe toxicities. HDMTX was discontinued in six and ten patients in each group, and the mean OS was 24.7 and 33 months. HDMTX is effective for elderly PCNSL patients. However, Group A had toxicities in patients with high pretreatment scores, and a toxicity scoring system was proposed.

PCNSL in patients aged over 60 should be treated based on the proposed pretreatment status score.

Keywords: *Primary Central Nervous System Lymphoma; Elderly Patient; Karnofsky Performance Status; Renal Function; Hematopoietic Potential.*

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of intracranial neoplasm, comprising less than 5% of all primary brain tumors [1, 2]. The aging of the population is a key factor in the epidemiology of PCNSL, with nearly half of patients being older than 60 years, and 10% being 80 years or older [3]. High-dose methotrexate (HDMTX)-based chemotherapy is an established therapy for PCNSL. Though there are several reports [4, 5] that have mentioned the effects of HDMTX on elderly patients with PCNSL, it is unclear whether elderly patients over 80 years of age should be treated in the same way as younger patients.

Managing PCNSL in patients over 80 is challenging. These elderly individuals often have multiple organ dysfunctions related to aging and comorbid illnesses that make them more vulnerable to HDMTX toxicity. Their underlying diseases also increase the probability of drug interactions that could lead to adverse events and reduced efficacy. A retrospective single-center review of elderly patients with PCNSL treated with HDMTX was conducted. The objective of this study was to elucidate the therapeutic outcomes and toxicities of patients over the age of 80 who received HDMTX by comparing them with patients aged between 60 and 80 years. Furthermore, a proposal is hereby made for a practical scoring system that would predict the risk of toxicity from HDMTX in elderly patients. This approach may contribute to the refinement of the HDMTX protocol for elderly patients with PCNSL.

2. Methods

From December 2008 to March 2015, sixteen patients aged over 60 years were treated for PCNSL at the Hokuto Hospital, Obihiro, Japan. Six patients were over 80 years old and 10 patients were between 60 and 80 years old. The diagnosis was proven by pathological study of

surgical biopsy specimens. Histopathologic diagnosis of malignant lymphoma, diffuse large B cell type, was confirmed in each patient. Positron emission tomography with 5-fluorodeoxyglucose, excluded systemic lymphoma in all cases. Laboratory examinations revealed no evidence of acquired immunodeficiency syndromes.

All patients were treated with HDMTX. Methotrexate was given intravenously at a dose of 3.5g/m^2, following the established regimen [6]. Leucovorin rescue was performed based on the serum methotrexate concentration. Additional treatment with Procarbazine and Vincristine were used according to the patient's general condition. Whole brain radiation was performed for patients in whom chemotherapy was insufficiently effective. The pretreatment status score (PRH score) was defined as follows: In the context of the Karnofsky performance scale (P), a score below 70 was designated as 1 point, thereby signifying a poor general condition. A creatinine clearance rate (Ccr) of less than 50 milliliters per minute is considered to be equivalent to one point, thereby indicating renal dysfunction (R). In the event of low counts in two or more hematopoietic lineages (H), the count is designated as one point, thereby indicating impaired hematopoietic function. The latter was defined as a white blood cell count of less than 5,000/μl, a red blood cell count of less than 4.5 × 10^6/μl, or a platelet count of less than 200 × 1000/μl (Table 1). The PRH score was documented for each patient based on assessments conducted at the time of admission prior to the initiation of chemotherapy. Scores of 2 or 3 points were categorized as high, 1 point as moderate, and 0 points as low.

The therapeutic response was evaluated using magnetic resonance imaging (MRI) with gadolinium-based contrast agents to obtain comprehensive whole-brain images. The clinical outcomes reported included the occurrence of National Cancer Institute-Common Toxicity Criteria (CTC) Version 2.0 grades III or IV (severe toxicities) and overall survival (OS). The severity of HDMTX-induced toxicities was evaluated through a combination of laboratory and physical examinations.

Table 1. *Definition and scoring of pretreatment status (PRH) score.*

Risk factor		Point	PRH (points)	Classification of score
P: low KPS	≤60	1	3	High
R: low Ccr (ml/min)	<50	1	2	
H: poor hematopoietic function	Multiple	1	1	Moderate
WBC (/μl)	<5000			
RBC (× 10^6/μl)	<4.5		0	Low
Platelets (× 1,000/μl)	<200			

KPS, Karnofsky performance score; Ccr, creatinine clearance; WBC, white blood cells; RBC, red blood cells; PRH, pretreatment status score calculated by the combined points for Karnofsky performance score (P), renal dysfunction (R), and hematopoietic function (H).

3. Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee in Hokuto hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

4. Results

Sixteen patients (mean age 74.6; range 60 to 85 years old), including 11 males (mean age 73.8; range 60 to 84 years old) and 5 females (mean age 76.4; range 70 to 85 years old), were treated with HDMTX. Six were treated with combined radiotherapy.

Clinical characteristics and conditions are summarized in Table 2. The treatment courses and outcomes for all patients are presented in Table 3. Profiles of patient number 1 to 6 were already published as cases report [7].

Table 2. *Summary of clinical characteristics and treatment outcomes of patients with primary central nervous system lymphoma by age group.*

Clinical status		over 80	60 to 80
Sex	Male	4	7
	Female	2	3

KPS	≥70	4	5
	≤60	2	5
Ccr	≥50 ml/min	4	9
	<50 ml/min	2	1
Hematopoietic function	High	2	5
	Low	4	5
CTC toxicity	≤Grade II	3	6
	≥Grade III	3	4
Response	CR	2	4
	PR	4	4
	PD	0	2
OS	≤1 year	3	3
	>1 year	3	7

Data are reported as numbers of patients.

KPS, Karnofsky performance score; Ccr, creatinine clearance; High hematopoietic function was defined as normal white blood cell, red blood cell and platelet counts and Low as any count below the normal level; CTC, National Cancer Institute-Common Toxicity Criteria (CTC) Version 2.0; Grade, CTC grade; CR, complete response; PR, partial response, PD, progressive disease; OS, overall survival.

Twelve patients (75%) had some at least some CTC grade of HDMTX toxicity. CTC grades III/IV toxicity occurred in 7 of the 16 patients (43%), 3 of 6 (50%) patients aged over 80 group (group A) and 4 of 10 (40%) aged 60 to 80 years (group B) (Table 4). Two patients (33%) in group A and 4 (40%) in group B showed a complete response to treatment, while chemotherapy had to be discontinued in 2 patients (33%) in group A and 3 patients (30%) in group B due to serious adverse events (Table 3).

Table 3. *Characteristics, additional treatment, and outcomes of patients with primary central nervous system lymphoma.*

Patient	Age	Gender	PRH	Treatment (times)	Response	Worst toxicity grade (type)	Survival (m)	
1	85	F	3	M (1)	PR	IV (thrombocytopenia)	0.6	deceased
2	84	M	2	MPV (2)	PR	IV (pancytopenia)	4.0	deceased
3	83	M	1	MPV (6) + RT	PR	IV (pancytopenia)	41.8	deceased
4	83	F	1	MPV (2)	CR	I (anorexia)	71.4	alive
5	83	M	1	MPV (4) + RT	PD	None	5.5	deceased
6	80	M	0	M (6) + RT	CR	None	24.7	deceased
7	78	M	3	MPV (1)	PD	IV (pancytopenia)	0.3	deceased
8	73	F	1	MPV (6)	PR	II (pancytopenia)	24.9	deceased
9	73	M	0	M (6) + RT	CR	I (anemia)	24.0	deceased
10	71	M	0	M (6)	CR	I (fever)	92.6	alive
11	71	F	2	MV (1)	PD	IV (pancytopenia)	0.3	deceased
12	71	M	1	MPV (3) + RT	PR	III (low Na)	29.8	alive
13	70	F	2	M (1)	PR	IV (pancytopenia)	0.6	deceased
14	67	M	1	MPV (4) + RT	PR	I (pruritus)	44.7	alive
15	62	M	1	MPV (4)	CR	None	35.7	alive
16	60	M	0	M (3)	CR	None	90.0	alive

PRH, pretreatment status score calculated by Karnofsky performance score (P), renal dysfunction (R), and hematopoietic efficacy (H); F, female; M in gender, male; M in treatment, methotrexate; P, procarbazine; V, vincristine; RT, radiation therapy; PR, partial response; CR, complete response; PD, progressive disease. In group A, severe toxicities were observed in both patients with a low KPS and in 1 of 4 (25%) patients with a high KPS. In group B, severe toxicities occurred in 4 of 5 (80%) patients with a low KPS but in none of the 5 with a high KPS. Severe toxicities were observed in all 3 patients with a low Ccr and in 4 of 13 (23%) with a high Ccr. In group A, severe toxicities were observed in both patients with a low Ccr and in 1 of 4 with a

high Ccr. In group B, severe toxicity occurred in the 1 patient with a low Ccr and in 3 of 9 (33%) with a high Ccr.

Severe toxicities occurred in 5 of 9 (55%) patients with hematopoietic dysfunction but in only 2 of 7 (29%) with higher blood counts. In group A, severe toxicities were observed in 2 of 4 (50%) with lower blood counts and in 1 of 2 (50%) with adequate blood counts. In group B, severe toxicities occurred in 3 of 5 (60%) patients with low blood counts and 1 of 5 (20%) with adequate blood counts. Treatment response to HDMTX was evaluated by contrast enhanced MRI of the whole brain. Complete response was achieved in 6 patients (2 in group A and 4 in group B), partial response in 7 patients (3 in group A and 4 in group B), and progressive disease was noted in 3 patients (1 in group A and 2 in group B) (Table 3). The mean overall survival (OS) in all patients was 30.4 months. In group A, the mean OS was 24.7 months, whereas that in group B was 33.0 months. While 6 patients out of the total (38%) showed a complete response, 5 of the 16 (31%) had no improvement, and their HDMTX therapy was stopped. Two patients (33%) in group A and 4 (40%) in group B had a complete response, while 2 (33%) in group A and 3 (30%) in group B discontinued HDMTX within two courses due to lethal toxicity. One 83-year-old woman (patient number 4) and her family wished to stop HDMTX after two courses, despite which, she had a complete response (Table 3).

Survival rate was visualized by Kaplan Meier curves in Figure 1. Group A and group B showed similar survival rate (Figure 1A).

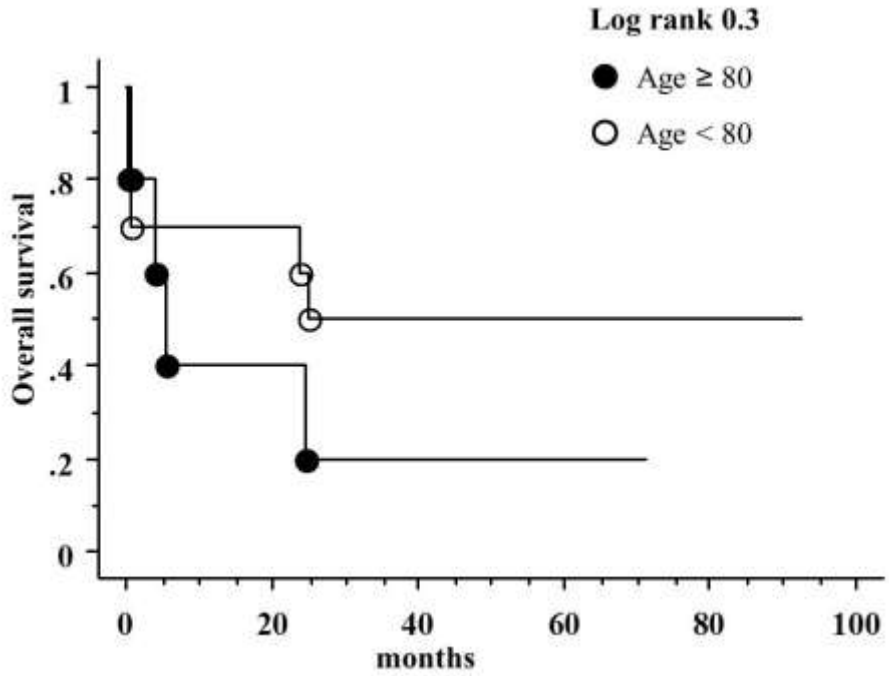

Figure 1. A. *Kaplan-Meier curves demonstrate overall survival in two distinct age groups of patients diagnosed with primary central nervous system lymphoma. The first group consists of patients aged over 80 years, while the second group comprises patients aged between 60 and 80 years. These patients underwent treatment with high-dose methotrexate-based chemotherapy.*

The average PRH score in all 16 patients was 1.2 (range 0–3). In group A, 2 patients (33%) had a high PRH score as did 3 in group B (30%). All 5 of these patients discontinued HDMTX because of severe cytotoxicity, and they all died with a mean OS 34.6 days (1.1 months). In contrast, the 11 patients with a moderate or low PRH score (0 or 1 point; 4 in group A and 7 in group B) continued HDMTX with a mean OS of 1346 days (44.9 months) (Table 4). In group A, severe toxicities were observed in both patients with a high PRH score and in 1 of 3 patients (33%) with a moderate PRH score. In group B, severe toxicities occurred in all 3 patients with a high PRH score but in only 1 of 4 (25%) with a moderate PRH score. No patients with a low PRH score had severe toxicity in either group A or group B (Table 4). Survival rate was clearly divided to two categories due to the PRH score. While high PRH score patients had poor prognosis, moderate and low PRH score patients kept longer survival period (Figure 1B).

Table 4. *Results of high dose methotrexate based–chemotherapy in each patient age group.*

Age	PRH	Patients (n)	mOS (m)	Severe toxicity (grades III or IV)
over 80	3	1	0.6	1 (100%)
	2	1	4.0	1 (100%)
	1	3	39.6	1 (33%)
	0	1	24.7	0 (0%)
60 to 80	3	1	0.3	1 (100%)
	2	2	0.4	2 (100%)
	1	4	33.8	1 (25%)
	0	3	68.9	0 (0%)

PRH, pretreatment status score calculated by Karnofsky performance score (P), renal dysfunction (R), and hematopoietic efficacy (H); mOS (m), mean overall survival (months)

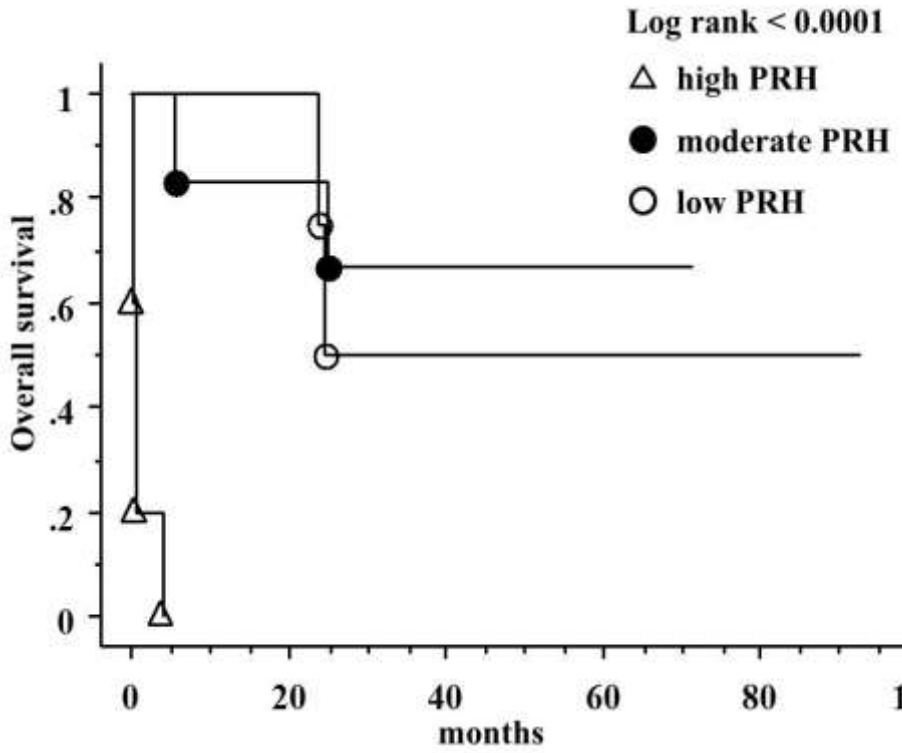

Figure 1.B. *Kaplan-Meier curves are presented, demonstrating overall survival in the three PRH classification groups (high, moderate, and low) of patients diagnosed with primary central nervous system lymphoma who underwent treatment with high-dose methotrexate-based chemotherapy.*

HDMTX-related toxicities were mainly observed in patients with a high PRH score at diagnosis, regardless of age (Table 4 and Figure 2). Even patients aged over 80 with a moderate PRH score generally did not have severe toxicity. Patient number 3, an 83-year-old man with a moderate PRH score, developed grade IV pancytopenia, but this patient still survived for over 3 years despite requiring dialysis, and achieved a partial response without any recurrence of PCNSL. Patients with moderate or low PRH scores in both groups had a relatively long OS (Figure 2)

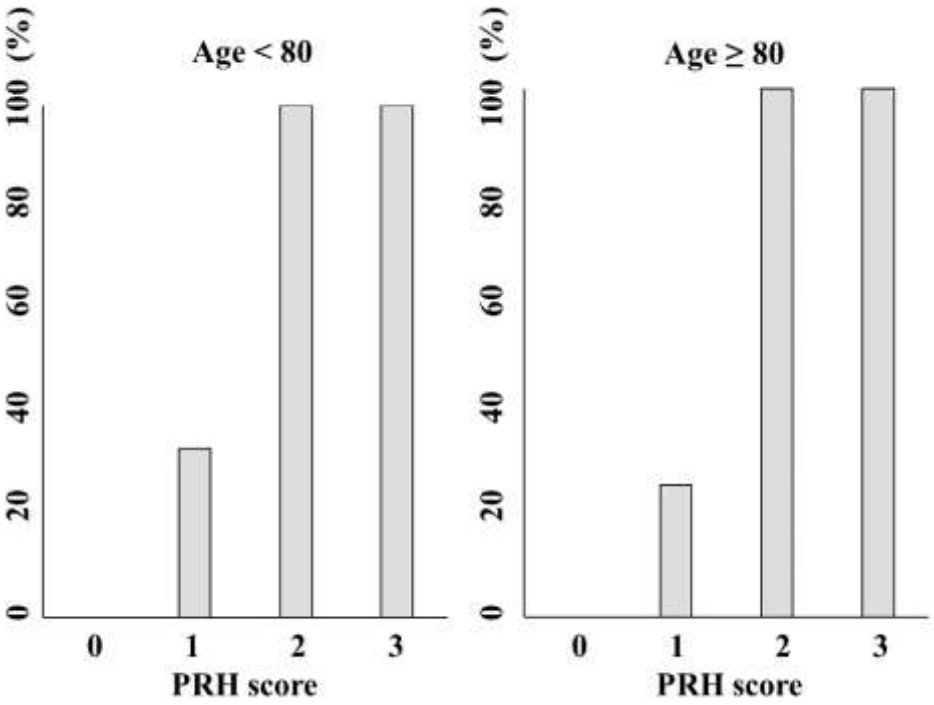

Figure 2. *Outcome of high-dose methotrexate-based chemotherapy by age group and PRH score. Graphs show overall survival and toxicity.*

5. Discussion

A comprehensive review of the extant literature reveals a consistent correlation between advanced age and a poor prognosis in cases of PCNSL [8-11]. A poor performance status has also been documented as a negative prognostic factor [8-10]. It has been demonstrated by several groups that HDMTX can be safely administered to elderly patients with adequate renal function [12-14]. The findings of this study corroborate the assertion that advanced age is but one critical factor to be taken into account when contemplating the utilization of HDMTX for the treatment of PCNSL.

In this study, patients with moderate or low PRH scores demonstrated a favorable clinical trajectory. Conversely, patients with a high PRH score exhibited an increased propensity for severe toxicities, which hindered the continuation of HDMTX treatment. Conversely, patients with a moderate or low PRH score demonstrated the capacity to persist with HDMTX. Ferreri et al. presented a widely utilized scoring system for PCNSL that aims to predict prognosis [9]. The International Extranodal Lymphoma Study Group (IELSG) scoring system has been demonstrated to predict survival outcomes in patients with extra nodal lymphoma. The system incorporates various prognostic factors, including age (greater than 60 years), performance status, elevated serum lactate dehydrogenase levels, high protein levels in cerebrospinal fluid, and the location of the lesion (in a deep brain region). These factors have been shown to independently predict survival outcomes in patients with extra nodal lymphoma. The analysis included patients who received treatment with multiple chemotherapy regimens, radiation therapy, or a combination of chemoradiation. The present study differs from others in that it analyzes only patients who received HDMTX-based therapy for PCNSL. Subsequently, the primary focus of this study was to examine the outcomes associated with HDMTX-induced toxicities and overall survival (OS). The PRH score employed in this study indicated the potential efficacy of HDMTX therapy and enabled the prediction of the probability of adverse events in elderly patients diagnosed with PCNSL. Furthermore, the PRH score is straightforward to calculate and does not necessitate invasive procedures, such as a lumbar puncture, in contrast to the prediction score reported in a previous study [11]. The following text is intended to provide a comprehensive overview of the subject matter. The findings of this study indicate that HDMTX can be administered to patients with low PRH scores, including those over 80 years of age. However,

its administration without modification may pose a significant risk to patients with high PRH scores. In contrast, Abrey demonstrated at the Memorial Sloan-Kettering Cancer Center (MSKCC) that age (more than 50 years) and performance status were identified as negative prognostic factors using a prognostic model scoring system [10]. The report concluded that age greater than 50 years is a negative prognostic factor. Given the observed rise in the prevalence of primary cutaneous anaplastic lymphoma (PCNSL) among elderly populations, the established 50-year age cut-off may prove to be an inadequate benchmark in forthcoming years. The present study focused on a cohort of elderly patients diagnosed with primary cutaneous anaplastic lymphoma (PCNSL). The analysis encompassed a cohort of over 70 patients diagnosed with primary cutaneous anaplastic large cell lymphoma (PCNSL). For the participants in this study, a considerably higher cutoff point for age is necessary. The following text is intended to provide a comprehensive overview of the subject matter. It is hereby proposed that the PRH score be assessed prior to the administration of treatment to elderly patients with PCNSL, including those who are over the age of 80. According to the PRH score, it is imperative that the HDMTX regimen be modified to ensure the safe continuation of chemotherapy, thereby facilitating a successful outcome. In the case of elderly patients with PCNSL who are at risk of poor survival, reducing the methotrexate dose or modifying the therapeutic protocol might be a viable option [15]. Patients with a high PRH score who are considered to be at high risk and for whom HDMTX therapy is being contemplated could be managed with careful treatment strategies. In addition, it is imperative to establish a modified methotrexate strategy for elderly patients with PCNSL who have a high PRH score. According to the literature, the reduced-dose methotrexate (MTX) treatment was expected to be recommended for elderly patients with primary central nervous system lymphoma (PCNSL) [7, 16, 17]. Further studies are required to establish appropriate doses and treatment schedules for methotrexate-based therapy for elderly patients.

Despite the findings suggesting a correlation between pretreatment PRH score and the manifestation of HDMTX-related toxicities, the study's limitations stem from the modest patient sample size. To substantiate a correlation between the PRH score and clinical outcomes with HDMTX-based treatment, a larger patient population will be required.

6. Conclusion

HDMTX may be effective against PCNSL in patients over 80. Pretreatment PRH score predicts severe HDMTX-related toxicities. Elderly patients with PCNSL should be treated with an appropriate strategy depending on their pretreatment PRH score.

7. Acknowledgements

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8. Conflict of Interest

There are no potential conflicts of interest to disclose. Author certify that he has no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock owner ship, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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