Glomerular Filtration Rate in Patients with Multiple Sclerosis Undergoing Stem Cell Transplantation and Treated With Cyclophosphamide

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ABSTRACT

Background: Glomerular filtration rate (GFR) is partially impaired in patients with multiple sclerosis (MS). When given chemotherapy before receiving hematopoietic stem-cell transplantation, GFR might be further deteriorated.

Objective: To measure the effect of cyclophosphamide on GFR in patients with MS who undergo chemotherapy.

Methods: We estimated GFR based on creatinine and cystatin C plasma concentrations in patients undergoing autologous hematopoietic stem-cell transplantation to treat their MS.

Results: Baseline GFR values were lower in the 28 patients with MS than in the 20 healthy individuals. Also, according to the Chronic Kidney Disease–Epidemiology Collaborative Group (CKD-EPI) 2012 Creat-CysC equation criteria, 4 of 28 patients were classified as having chronic kidney disease (CKD) before receiving the chemotherapy drugs. After receiving 4 × 50 mg per kg body weight cyclophosphamide, abnormal GFR results were recorded in 12 of 28 patients.

Conclusions. Renal function must be monitored in patients with MS undergoing autologous stem-cell transplantation. Also, chemotherapy should be constrained as much as possible to prevent further deterioration of renal function.

Keywords: multiple sclerosis, glomerular filtration rate, cyclophosphamide, renal function, stem cell transplantation, nephrotoxicity

Glomerular filtration rate (GFR) has been found to be compromised in patients with multiple sclerosis (MS).[1] The origin of renal failure in this disease can be attributed to neurogenic bladder, iatrogenic decreased renal perfusion, acute tubular necrosis, or allergic interstitial nephritis.[2,3] Many of the drugs used to treat MS have the potential adverse effect of infections; therefore, such patients need antibiotic therapy.

Antibiotics are the primary cause of drug-associated nephropathy. They are responsible for acute interstitial nephritis, also known as acute tubulointerstitial nephritis, due to 1 of 2 different pathophysiologic mechanisms: a drug-induced immunologic process or direct action due to drug accumulation.[4]

Another possible cause for renal damage in these patients is chemotherapy. Patients undergoing hematopoietic stem cell transplantations (HSCTs) receive chemotherapy. Despite dramatic improvements in patient survival and drug tolerability, nephrotoxicity remains an important complication of these drugs. Adverse renal effects occur because of innate drug toxicity and a number of patient-related factors.[5]

Abbreviations

GFR, glomerular filtration rate; MS, multiple sclerosis; HSCTs, hematopoietic stem cell transplantations; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; EDSS, Expanded Disability Status Scale; PBSC, peripheral blood stem-cell; Cy, cyclophosphamide; G-SCF, granulocyte-colony stimulating factor; CD, cluster of differentiation; CKD-EPI, Chronic Kidney Disease–Epidemiology Collaborative Group; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; S_{cys}, standardized serum cystatin C KDIGO, Kidney Disease: Improving Global Outcomes; CKD, chronic kidney disease; HSC, hematopoietic stem cell; C_{max}, maximum plasma concentration achieved after a given dose;, AUC, area under the curve

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Patients with MS are treated with autologous HSTC, with the rationale of resetting their immune system after in vivo purging of self-reactive immune cells.[6] Because HSCT is not a first-line therapeutic option, it is common that patients seeking this approach have been previously treated with immunosuppressant drugs and antibiotics to treat or prevent infections. Therefore, these patients might be found to have renal function impairment before HSCT treatment. Also, graft conditioning with cyclophosphamide might further damage renal function because the kidneys are a major elimination pathway for this antineoplastic drug and its metabolites.[7–9]

In this study, we measured GFR in patients with MS undergoing autologous HSCT before and after receiving cyclophosphamide as part of the graft-conditioning regimen. Reporting on the efficacy and safety of HSCT in MS is beyond the scope of this article.

Materials and Methods

Patients

Twenty-eight white patients (20 of whom were women) with MS were recruited for participation in this study. Of these 28 patients, 6 had relapsing-remitting MS (RRMS), 18 had secondary progressive MS (SPMS), and 4 had primary progressive MS (PPMS). To be admitted to the treatment program, patients needed to have Karnofsky performance status[10] of higher than 70% and an Expanded Disability Status Scale (EDSS) score[11] of 7 or less in the 2 weeks before transplantation. Ages ranged from 29 to 67 years, with a median of 51.5 years. Patient EDSS scores ranged from 1.00 to 7.00, with a mean value of 5.39 and a median value of 5.75.

Conditioning and Hematopoietic Stem-Cell Transplantation

Recruitment of hematopoietic progenitor cells from the bone marrow to the peripheral blood after treatment with chemotherapy and/or cytokines is called *mobilization*. The release of these cells from the bone marrow is a physiological phenomenon that protects hematopoietic progenitor cells from toxic injury—circulating cells can re-engraft bone marrow. Peripheral-blood stem-cell (PBSC) mobilization was accomplished with cyclophosphamide (Cy) and granulocyte-colony stimulating factor (G-CSF). Autologous hematopoietic stem cells were harvested from peripheral blood by means of leukapheresis and enumerated using standard flow cytometry procedures, as described in the literature.[6,12] As an outpatient form of treatment, and after collecting the targeted number of peripheral blood cluster of differentiation (CD)34+ cells, intravenous Cy (50 mg/kg) was delivered during a 120-minute period on days –2 and –1, followed by sodium 2-mercaptoethanesulfonate (1000 mg/m^2 during a 180-minute period); ondansetron, 8 mg, dexamethasone, 4 mg; and pantoprazole, 40 mg.

Hematopoietic stem-cell-harvest apheresis is now the primary method for obtaining the cells that are grafted in the bone marrow transplantation procedure. The blood is separated, and mononuclear white blood cells, which include mobilized stem cells, are transferred to a collection bag, while the other blood components circulate back into the body of the patient through a return needle. Autologous hematopoietic stem cells were harvested from peripheral blood, as described earlier herein

Apheresis products obtained on day –1, were reinfused to the patients on day 0 after storage in a conventional blood-bank refrigerator (Thermo Scientific Forma Undercounter 3626 Blood Bank Refrigerator. Serial # 501080, Thermo Fisher Scientific). Once the apheresis was completed, and after the administration of the intravenous Cy, patients received ondansetron (4 mg every 12 hours after chemotherapy), oral cotrimoxazole (800 mg [160 mg every 24 hours]), oral fluconazole (200 mg), and oral acyclovir (400 mg every 12 hours) until the granulocyte value was greater than 0.5×10^9 per L. During this period, all patients received a clinical examination and laboratory workup every 48 hours. The cumulative dose of Cy was 200 mg per kg, divided into 4 batches of 50 mg per kg each.

After the granulocyte recovery, patients were given rituximab (375 mg/m^2 during a 3-hour period). As prophylaxis against infections and MS relapses, in the following 6 months, cotrimoxazole, 800 mg (160 mg twice per day, 3 times per week); acyclovir, 800 mg daily; and rituximab, 100 mg every 2 months during a 12-month period were recommended. After grafting and recovery of granulocytes, patients were given rituximab (375 mg/m^2) and afterwards, 100 more mg every 2 months during a 12-month period.

The transplantation protocol was approved by the Ethics Committee of Laboratorios Clinicos de Puebla and Centro de Hematología y Medicina Interna, Puebla,

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México, in accordance with the Helsinki Declaration of 1975 (CONBIOETICA 21CEI 001 201 30605, Reg.13 CEI 21114126). The study protocol is registered as ClinicalTrials.gov identifier NCT02674217.

Glomerular Filtration Rate

The Chronic Kidney Disease–Epidemiology Collaborative Group (CKD-EPI) has recently developed an equation that uses creatinine and cystatin C values. This equation has proven to have the smallest bias, compared with other reference methods.[13–15]

$$\begin{aligned} \text{eGFR} = {} & 135 \times \min\left(S_{Cr}/\kappa,\ 1\right)^{\alpha} \times \max\left(S_{Cr}/\kappa,\ 1\right)^{-0.601} \\ & \times \min\left(S_{cys}/0.8,\ 1\right)^{-0.375} \\ & \times \max\left(S_{cys}/0.8,\ 1\right)^{-0.711} \times 0.995^{\text{Age}} \\ & \times 0.969\ [\text{if female}] \times 1.08\ [\text{if black}] \end{aligned}$$

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

S_{Cr} (serum creatinine) = mg/dL

S_{cys} (standardized serum cystatin C) = mg/L

κ = 0.7 (females) or 0.9 (males)

α = –0.248 (females) or –0.207 (males)

$\min(S_{Cr}/\kappa \text{ or } 1)$ = indicates the minimum of S_{Cr}/κ or 1

$\max(S_{Cr}/\kappa \text{ or } 1)$ = indicates the maximum of S_{Cr}/κ or 1

$\min(S_{cys}/0.8, 1)$ = indicates the minimum of $S_{cys}/0.8$, 1

$\max(S_{cys}/0.8, 1)$ = indicates the maximum of $S_{cys}/0.8$, 1

age = years

This equation was used to estimate GFR in all patients before and 2 weeks after the administration of Cy. We measured plasma creatinine levels using a commercial method (CREm, Lot No. M708022; UniCel DxC 800 Synchron Clinical System; Beckman Coulter, Inc). This method is a kinetic modification of the Jaffe procedure, in which creatinine reacts with picric acid at alkaline pH.[16] We determined cystatin C levels using a commercial immunoassay (N Latex Cystatin C Immunoassay, Lot 47738; BN Prospect; Siemens AG).[17] We used a group of 20 healthy individuals as a control population.

Statistical Analysis

We compared GFR values between control individuals and patients using the Student's *t*-test for independent observations, and among the patients before and after receiving chemotherapy using the Student's *t*-test for paired observations. Correlation of GFR with other parameters was assessed by linear regression analysis. In all instances, an α value of 0.05 was considered the limit of statistical significance. We calculated statistics with the aid of MedCalc statistical software (MedCalc Software bvba).[18]

Results of the efficacy and safety of HSCT in MS in a larger number of patients will be published elsewhere. Such results are beyond the scope of this article.

Results

Pretreatment GFR in Patients with MS

Mean GFR values were lower in the MS group before any treatment, compared with those values in 20 healthy controls whose values we studied simultaneously (mean [SEM], 105.60 [3.05] and 147.60 [3.44] mL/min/1.73 m^2, respectively; t = 9.050, P <.001).

According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines,[19] 4 patients with MS were tagged as having "mildly decreased GFR" because they had values of less than 90 mL per minute per 1.73 m^2 but greater than 60 mL per minute per 1.73 m^2. Those patients, therefore, had low risk for developing CKD.

There was a statistically significant negative correlation (P = .006) between age and GFR; however, GFR values were not associated with EDSS score or time elapsed since diagnosis of MS. **Figure 1** shows this tendency and the respective equation.

Effect of Treatment on GFR

As shown in **Figure 2**, in all but 7 patients, GFR values decreased. Mean (SEM) values before and after treatment were significantly different (105.60 [3.05] vs 94.53 [3.56];

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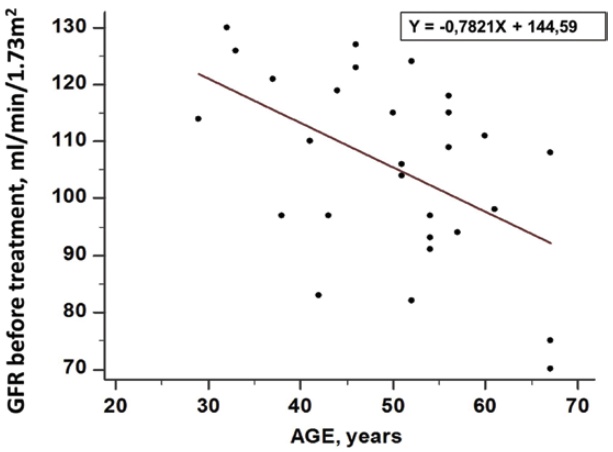

Figure 1

Correlation between age and glomerular filtration rate (GFR) in 28 patients with multiple sclerosis (MS) before autologous hematopoietic stem-cell transplantation.

$t = -4.029$, $P < .001$). Also, besides the 4 patients that had mildly decreased GFR, 8 more case individuals who first had had normal values (>90 mL/minute/1.73 m^2) ended up with mildly decreased GFR (≤90 mL/min/1.73 m^2) after chemotherapy. In no instance were GFR values less than 60 mL per minute per 1.73 m^2. After 2 more weeks of follow-up, 16 of the 21 patients had decreased GFR values after Cy therapy had returned to baseline values. No further GFR follow-up was performed, but none of the patients has developed CKD after 12 to 24 months.

Discussion

There are 2 principal pathways for drug excretion by the kidney, namely, glomerular filtration and tubular secretion. The former plays a major role in the elimination of non–protein-bound small molecules, whereas molecules that are protein-bound enter the urine by secretion in the proximal tubule. For drugs in which renal excretion is an important determinant of elimination of the intact drug or an active metabolite, such as cyclophosphamide, dose adjustment is often required if renal function is impaired. Although the prevalence of elevated serum creatinine levels is rare in patients with cancer, the prevalence of a reduced GFR is relatively high.[7,8]

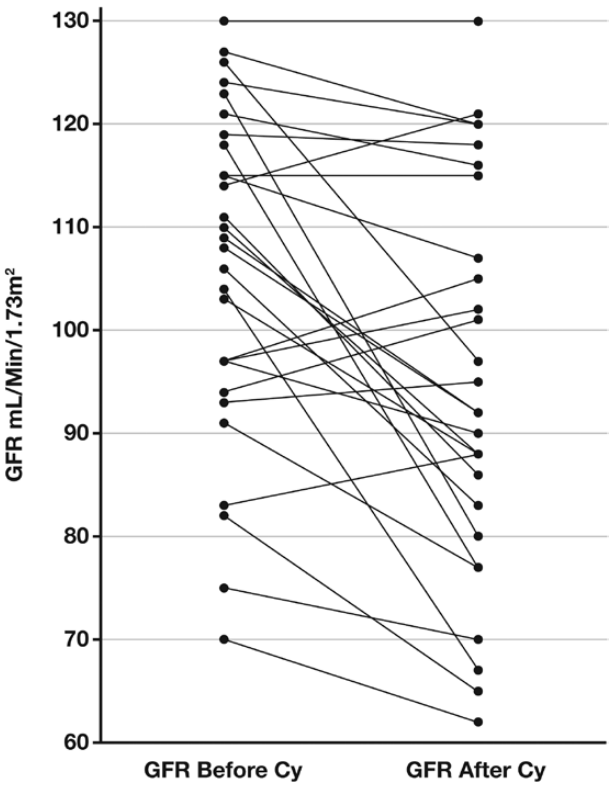

Figure 2

Glomerular filtration rate (GFR) in 28 patients with multiple sclerosis (MS) before and 2 weeks after receiving a total cumulative dose of 200 mg per kg of cyclophosphamide (Cy).

Impaired renal function in patients with MS has been documented in the past. Therefore, it is necessary to keep in mind that this finding might have implications for treatment of these patients with nephrotoxic drugs.[1]

Cy has been shown to be an effective regimen for hematopoietic stem cell mobilization in patients undergoing autologous stem cell transplantation. However, the optimal dose to be used, which maximizes hematopoietic stem cell (HSC) collection yields while minimizing febrile neutropenia and other toxicities, remains controversial.[9]

We compared 2 historical cohorts of patients with non-Hodgkin lymphoma who received G-CSF and Cy, at a dose of 4 g per m^2 or 2 g per m^2. Although both regimens were effective in mobilizing stem cells, mobilization efficacy and toxicity vary greatly. Higher doses resulted in higher HSC yields requiring fewer apheresis procedures;

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however, this benefit was offset by increased morbidity and hospitalization.[20]

The therapeutic range for Cy has been reported to be 10 μg per mL to 25 μg per mL. Its half-life is 4 to 8 hours[20] and, as in the vast majority of drugs, its toxicity is related to plasma concentrations. Hence, toxicity is related to the maximum plasma concentration achieved after a given dose (C_{max}), rather than to the total amount of bioavailable drug reflected as the area under the (pharmacokinetic) curve (AUC).[21] By splitting the total Cy dose into 2 dosages, we aim to achieve sufficient immunosuppression, given that the amount of bioavailable Cy is comparable to that obtained by a single dosage administration, whereas toxicity is limited because each of the C_{max} values is considerably lower.

When dealing with patients who have MS, the renal toxicity of cyclophosphamide deserves special attention because GFR is already compromised in a large proportion of these patients. In our experience, using a total dose of Cy of 200 mg per kg (2 × 50 mg infusions before apheresis and 2 × 50 mg more after apheresis), we were able to mobilize and collect at least 1 × 106 CD34+ cells per kg in a single apheresis procedure in 4 of 5 patients. The toxicity was very low—only 8 of 286 patients have needed hospitalization, no opportunistic infections have been recorded, and none of the patients has died as a complication of the HSCT.[6]

Our low-intensity conditioning regimen, therefore, is efficient in mobilizing stem cells and is less toxic than other therapeutic modalities, balancing mobilization safety, efficacy, and cost. The results of this work emphasize the need to constrain chemotherapy toxicity as much as possible because of the strong potential of iatrogenic CKD. **LM**

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