Substitution of Oral for Intravenous Cyclophosphamide in Membranous Nephropathy

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Abstract

Background Optimal immunosuppressive treatment for membranous nephropathy is still a matter of controversy. Current recommendations include oral cyclophosphamide combined with steroids (modified Ponticelli regimen) as first-line treatment in patients who are high risk. However, concerns about the cumulative toxicity of oral cyclophosphamide persist. In the last 30 years, a protocol based on low-dose intravenous cyclophosphamide plus steroids has been used to treat membranous nephropathy in Uruguay. We aimed to assess the efficacy of this regimen to induce clinical remission in patients with membranous nephropathy.

Methods In this retrospective, observational cohort study, we analyzed the outcome of 55 patients with membranous nephropathy treated between 1990 and 2017 with a 6-month course of alternating steroids (months 1, 3, and 5) plus intravenous cyclophosphamide (single dose of 15 mg/kg on the first day of months 2, 4, and 6).

Results At 24 months, 39 (71%) patients achieved clinical response with complete remission observed in 23 patients (42%) and partial remission in 16 (29%). Median time to achieve partial and complete remission was 5.9 and 11.5 months, respectively. Absence of response was observed in 16 patients (29%), five of whom started chronic RRT after a median follow-up of 3.5 years. Clinical relapse occurred in nine of 33 (27%) patients at a median of 34 months after treatment discontinuation.

Conclusions Replacement of oral cyclophosphamide with a single intravenous pulse on months 2, 4, and 6 of the modified Ponticelli regimen can be an effective and safe alternative for treatment of membranous nephropathy.
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Introduction

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. The usual clinical presentation is a full nephrotic syndrome with preserved kidney function (1). Considering that about a third of patients undergo spontaneous remission and a third progress to ESKD, the optimal management of MN is still a matter of debate (2–8). The identification of the M-type phospholipase A_2 receptor (PLA2R) and thrombospondin type 1 domain–containing 7A as glomerular antigens involved in the pathogenesis of primary MN have improved our understanding of the mechanisms of disease (9,10). Furthermore, the elucidation of an autoimmune etiology has led to a renewed enthusiasm in the role of immunosuppressive therapy (11). Current international guidelines recommend a 6-month course of alternating monthly cycles of intravenous (IV) and oral steroids (ST) plus oral cyclophosphamide (CYC), the modified Ponticelli regimen, as first-line therapy in patients at high risk of progression to ESKD (12–14). Nevertheless, there is great concern about the toxicity induced by high doses of CYC as a consequence of regimens based on oral administration. A relatively recent analysis showed a three-fold increase in cancer risk in patients with MN who received oral CYC compared with controls (15). Additionally, another contemporary study reported significantly fewer adverse events in patients treated with rituximab compared with patients who received oral CYC-based regimens (16). However, it is important to emphasize that the mean cumulative dose of CYC in the latter studies was considerably high (between 18

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and 37 g). This might explain, at least in part, the large number of adverse events observed in patients treated with CYC.

During the 1990s, Uruguay had poor availability of oral CYC and, consequently, the implementation of the modified Ponticelli regimen required substitution with IV CYC. The aim of this study was to analyze the efficacy and long-term outcomes of treatment with low-dose IV CYC plus steroids in a cohort of patients with biopsy sample–proven MN (17,18).

Materials and Methods

Patient Population

A total of 55 patients with a biopsy sample–proven diagnosis of MN who were treated with alternating steroids plus low-dose IV CYC between 1990 and 2017 were included. Patients with clinical, histologic, or serologic evidence of secondary MN were excluded. Secondary causes were excluded as per standard policy, including a complete medical history and physical exam; history of drugs used; chest x-ray; kidney ultrasound; hepatitis B, hepatitis C, and HIV status; treponemal test; antinuclear antibodies; and screening for occult malignancy (according to age and sex). All patients had new-onset MN; hence, none of them had previously received immunosuppressive treatment. The study was approved by the Ethics Committee at the School of Medicine, Clinical Hospital Dr. Manuel Quintela.

Treatment Regimen

All patients received a 6-month course of alternating monthly steroids plus CYC, as described in the modified Ponticelli regimen, but CYC was administered intravenously instead of orally (15 mg/kg IV single dose on day 1 of months 2, 4, and 6). CYC initial dose was decreased by 2.5 mg/kg in patients >60 years and 5 mg/kg in patients >70 years; and it was decreased by 2.5 mg/kg if serum creatinine was >2.7 mg/dl. Subsequent doses were adjusted to achieve a 2-week nadir leukocyte count of >3000/mm^3. None of the patients received a total cumulative dose of >3 g of CYC. The steroid protocol was administered during months 1, 3, and 5 and included 20 mg/kg IV methylprednisolone (maximum 1 g) daily for three doses (days 1, 2, and 3), and then oral prednisone (0.5 mg/kg per day) for 27 days, followed by a quick tapering (10 mg/wk). Treatment with angiotensin-converting enzyme inhibitors. has been formally indicated in national protocols since the 1990s. IV 2-mercaptethanesulfonate was used as prophylaxis of CYC-induced hemorrhagic cystitis.

Definitions and Follow-up

Complete remission (CR) was defined as proteinuria of <300 mg per 24 hours. Partial remission (PR) was defined as a reduction in proteinuria of at least 50% from baseline plus final proteinuria between 300 and 3500 mg per 24 hours. No remission (NR) was defined as proteinuria >3500 mg per 24 hours. Relapse was defined as the development of proteinuria of >3500 mg per 24 hours after achieving CR or PR. eGFR was calculated with the CKD–Epidemiology Collaboration equation. Severe adverse events during treatment

were assessed, including hospital admissions due to infections and myelosuppression that required granulocyte–colony stimulating factor or blood transfusions. Cancer incidence was evaluated as a long-term adverse effect of CYC.

Outcomes

The primary outcome was clinical remission (partial or complete) at 24 months. Secondary outcomes included incidence of relapse, progression to ESKD, and severe treatment-related adverse events.

Statistical Analyses

Quantitative variables were described as medians and interquartile ranges. The Kolmogorov–Smirnov test was used to test the normality of distributions. Because variables were not normally distributed, groups were compared using the Mann–Whitney or Kruskal–Wallis test as required. Categoric variables were described as frequencies and percentages and were analyzed using the chi-squared test. Kidney survival was estimated using the Kaplan–Meier method, and log-rank tests were used to compare survival distribution. All statistical tests were two sided, and differences were considered significant with a P value <0.05. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Co., Armonk, NY).

Results

Demographics and baseline clinical characteristics of patients according to treatment response are detailed in Table 1. A total of 38 (69%) patients were men, with a median age at the time of kidney biopsy of 53 years. Median serum creatinine at clinical presentation was 1.0 mg/dl (interquartile range [IQR], 0.79–1.28) and median proteinuria was 7.6 g/24 h (IQR, 4.5–11.2). Median baseline systolic and diastolic BP were 130 mm Hg (IQR, 111–140) and 80 mm Hg (IQR, 70–90), respectively. Although no significant differences were observed, baseline eGFR was lower and proteinuria was higher in the group that did not respond to treatment.

Primary Outcome

At 24 months, 39 (71%) patients achieved clinical response; there was CR in 23 (42%) of patients and PR in 16 (29%). NR was observed in 16 (29%) patients. Detailed outcome of clinical response at 6–24 months is presented in Table 2. In the group that achieved CR, proteinuria decreased from 6.3 g/24 h (IQR, 3.7–8.6) to 0 g/24 h (IQR, 0–0.17) (P<0.001); in the PR group, proteinuria decreased from 8.0 g/24 h (IQR, 4.5–13.3) to 1.1 g/24 h (IQR, 0.7–1.7) (P<0.001). Proteinuria levels in patients without treatment response were 6.8 g/24 h (IQR, 5.1–10.0). The median time from kidney biopsy to treatment onset was 2.7 months (IQR, 1.8–5.4). The median time between treatment and clinical response was 5.9 (IQR, 4.6–16.0) and 11.5 (IQR, 5.9–15.0) months to achieve PR and CR, respectively. Response rate (CR plus PR) reached 76% at month 12 after treatment, however, two patients relapsed before month 24; thus, the response rate decreased to 71% (Table 2).

Table 1. Baseline clinical characteristics of the study cohort according to remission

Variable	All	Remission			P
		Complete	Partial	No remission	
Number, n (%)	55 (100)	24 (44)	18 (33)	13 (24)	
Men, n (%)	38 (69)	15 (63)	12 (67)	11 (85)	0.37
Age, y (IQR)	53.0 (38–64)	52.5 (33.3–66.8)	49.5 (32.0–59.5)	57 (39–65)	0.43
Proteinuria, g/24 h (IQR)	7.6 (4.5–11.2)	6.3 (3.7–8.6)	8.0 (4.5–13.3)	8.8 (6.8–12.5)	0.16
Creatinine, mg/dl (IQR)	1.0 (0.8–1.3)	0.9 (0.8–1.2)	0.9 (0.0–1.3)	1.2 (1.0–2.1)	0.05[a]
eGFR, ml/min (IQR)	81 (5–99)	86 (73–110)	87 (80–110)	67 (30–86)	0.19
SBP, mm Hg (IQR)	130 (111–140)	130 (110–142)	125 (116–148)	120 (100–143)	0.59
DBP, mm Hg (IQR)	80 (70–90)	80 (70–90)	80 (70–90)	75 (60–83)	0.52

Values are expressed as median (IQR) or n (%). IQR, interquartile range; SBP, systolic BP; DBP, diastolic BP.
[a]Significant difference between complete remission and no remission groups ($P=0.01$, Mann–Whitney test).

Secondary Outcomes

Median follow-up of the entire cohort was 7.1 years (IQR, 3.2–13.9). During the study period, nine (16%) patients were lost to follow-up; therefore, analysis of relapse rate included a total of 33 patients. After treatment discontinuation, relapse occurred in five of 19 (26%) patients with CR, and in four of 14 (29%) patients with PR (Figure 1). This relapse rate (27%; nine of 33) should be interpreted in the context of the long follow-up period of those 33 patients (85.2 months; IQR, 42.6–159.3). Considering only the first 24 months after treatment, only two of 33 (6%) patients relapsed. Both patients relapsed on month 12 after treatment. The median time between treatment and relapse was 34 months (IQR, 18–67) (Figure 2).

Over the course of the entire follow-up period, five of 46 (11%) patients progressed to ESKD in a median time of 3.5 years (IQR, 2.3–10.1) since kidney biopsy. All of these patients were included in the NR group (Figure 3). Baseline serum creatinine was higher in the group of patients that developed ESKD (2.32 mg/dl [IQR, 1.75–3.55] versus 0.95 mg/dl [IQR, 0.79–1.20]), although the difference was NS ($P=0.15$). Baseline proteinuria was similar in the ESKD group (6.9 g/24 h; IQR, 3.5–14.2) and in subjects that did not require chronic RRT (7.8 g/24 h; IQR, 4.7–11.5) ($P=0.67$). On the other hand, patients that achieved CR or PR had significantly better kidney survival than those with NR ($P=0.002$) (Figure 2). Median follow-up of patients with clinical response that did not progress to ESKD was 7.2 years (IQR, 3.5–14.9).

Adverse Events

None of the patients required blood transfusions or granulocyte–colony stimulating factor for the management of myelosuppression. One patient developed community-acquired pneumonia 2 weeks after the first CYC dose and required hospital admission. When the infection improved, immunosuppressive treatment was successfully completed. Three patients (7%) were diagnosed with cancer: two cases of basal cell carcinoma of the skin and one case of multiple myeloma (de novo). Time between the first CYC bolus and the oncologic diagnosis was 3 and 11 years, respectively, for the patients with skin cancer, and 7 years for the patient with multiple myeloma. Five patients died during follow-up

at 1, 7, 13, 15, and 18 years after MN diagnosis. The median age at death was 71 years (IQR, 42–82).

Discussion

In this retrospective, observational study, we found that the substitution of oral with low-dose IV CYC in the modified Ponticelli regimen can be an effective and safe option for treating patients with MN. It should be noted that we analyzed a proven therapy for MN by a different dose and route. The efficacy of cytotoxic drugs in the management of MN has already been demonstrated (19,20); nonetheless, the risk of malignancy is still a matter of concern. One of the main drawbacks of using oral CYC is a high cumulative dose with potential serious adverse effects. Our study shows that the use of IV CYC has the advantage of a significantly lower cumulative dose without losing efficacy. Of the 55 patients included in our cohort, >75% achieved a clinical response (CR plus PR) after 1 year. Additionally, it is reasonable to assume that the substantial reduction in proteinuria (far below the nephrotic range) in patients who attained PR had a positive effect on kidney prognosis. Although relapse occurred in 27% (nine of 33) of the patients, it is important to emphasize that even patients who experienced a relapse remained on remission for almost 3 years. The importance of remission duration on outcome has been previously stated by other authors (21). Kidney survival after a median follow-up of 7.1 years was excellent (90%). In fact, none of the patients that achieved CR developed ESKD throughout the follow-up period.

Table 2. Outcome of complete and partial remission at 6–24 months

Months	CR and PR (%)	CR (%)	PR (%)
6	69	20	49
12	76	33	44
18	71	38	33
24	71	42	29

Values express the percentage of patients on remission at 6, 12, 18, and 24 mo after treatment. CR, complete remission; PR, partial remission.
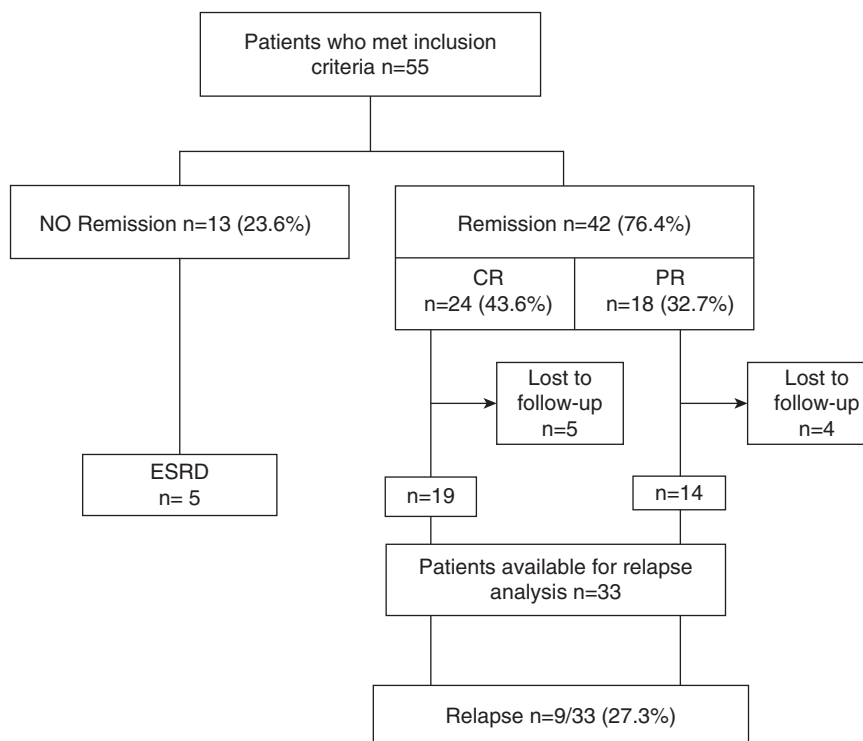
Figure 1. | **Flowchart of the study.** CR, complete remission; PR, partial remission.

Baseline serum creatinine has been described as a significant, independent predictor factor for spontaneous remission and a predictor factor for response to treatment (5). In line with this, we observed higher baseline creatinine values in those patients who did not exhibit a treatment response. On the other hand, the incidence of cancer was lower than that reported for oral CYC (15,16,22,23).

Current Kidney Disease Improving Global Outcomes guidelines recommend steroids plus cyclical oral CYC as first-line therapy in patients with MN who are high risk (12). In the landmark study by Ponticelli *et al.* (19), where a 6-month course of alternating ST plus chlorambucil was compared with ST plus oral CYC, CR or PR was achieved in 93% of the patients in the CYC arm (versus 82%) after a median

follow-up of 42 months. Relapse occurred in 25% of the patients (versus 30% in the chlorambucil group) between 6 and 30 months after initial therapy. Subsequently, in
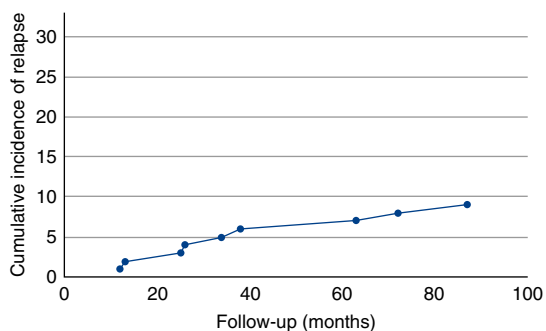

Figure 3. | **Long-term kidney survival of patients with complete, partial and no remission.** Five patients (10.8%) progressed to ESKD in a median time of 3.5 years since kidney biopsy. Of note, all of them were included in the NR group. NR, no remission.

Figure 2. | **Incidence (number of patients) of relapse during follow-up.** Relapse occured in nine patients, two of them within the first 24 months after treatment. The median time between treatment and relapse was 34 months (IQR, 18–67).
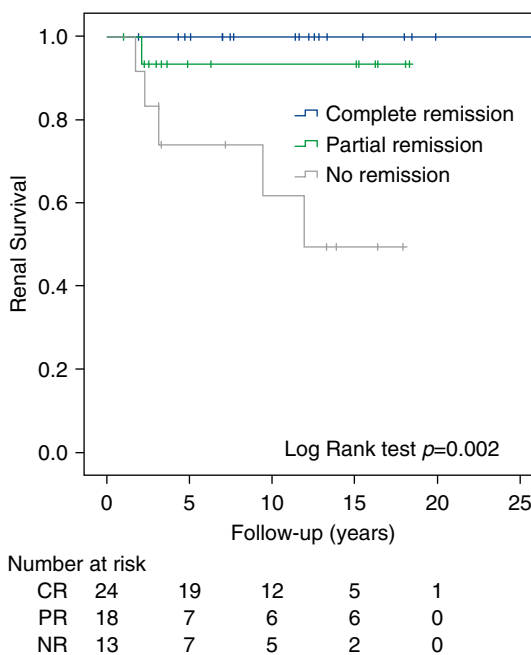
a prospective, randomized trial by Jha et al. (20), a similar scheme of ST plus oral CYC was compared with a control group that received supportive treatment only. Clinical response was attained in 72% of the patients (CR, 15; PR, 19) in the ST plus CYC arm versus 35% in the control group. Median follow-up duration was 11 years and relapses were noted in eight of 34 (24%) patients in the ST plus CYC group. Remarkably, kidney survival at 10 years was considerably superior in the experimental group (89% versus 65%) (20).

Adverse effects associated with alkylating agents, particularly the increased risk of cancer, represent a great concern and may restrict the use of this highly effective therapeutic option. CYC has been related to infections, bladder toxicity, myeloid dysplasia, and nonmelanoma skin cancer. As recently stated by Ponticelli et al. (7), the oncogenic risk is related to the intensity and length of the treatment and to the use of other immunosuppressive agents. In patients with MN, van den Brand et al. (15) reported that the risk of malignancy in CYC-treated subjects was approximately three times higher compared with those not exposed to CYC. Over a median follow-up period of 6 years, the observed cancer incidence was 21.2 per 1000 person-years in patients treated with CYC versus 4.6 per 1000 person-years in the control group, resulting in crude and adjusted incidence ratios of 4.6 and 3.2, respectively. However, it is important to mention that the median cumulative dose of CYC received by patients in the aforementioned study was 37 g (15). This remarkably high cumulative dose must be considered when analyzing potential CYC toxicity because the usual cumulative dose in the modified Ponticelli regimen is approximately 9–13 g. Of note, the protocol described in our study enables a substantial reduction of the total cumulative CYC dose compared with the oral or even the monthly IV protocols recently described by other authors (24–26).

Outside the setting of MN, follow-up data from the European Vasculitis Study Group clinical trials suggested that the less-extensive use of immunosuppressive drugs might result in a lower cancer risk compared with historical studies (23). Interestingly, in a study that compared pulse versus daily oral CYC for induction of remission in ANCA-associated vasculitis (the CYCLOPS trial), no differences were found between the two groups with regard to the incidence of malignancy. After a median follow-up of 4.3 years, 10% of patients in the oral CYC group versus 12% in the IV CYC group developed cancer (27).

It is reasonable to assume that a decrease in the total cumulative dose of CYC may reduce its adverse effects. In this study, we have addressed the oncologic risk of CYC over a period of 8.9 ± 6.3 years and found only three cases of cancer, none of which affected the urinary tract. The long observation period between kidney biopsy and the occurrence of malignancy virtually excludes the possibility that a diagnosis of cancer may have been missed at the time of MN presentation.

To date, there are few reports that have explored the effectiveness of IV CYC in the setting of MN. A study from 1992 concluded that treatment with steroids plus IV CYC ($n=13$) compared with steroids alone ($n=13$) did not improve kidney function in patients with deteriorating kidney function or persistent proteinuria. In both groups, the same number of patients progressed to ESKD and required

chronic dialysis during follow-up (28). Notably, all patients had an elevated serum creatinine level before starting immunosuppressive therapy (2.7 ± 1.6 mg/dl steroids versus 2.3 ± 1.0 mg/dl CYC plus steroids). A similar analysis reported by Reichert et al. (29) compared the efficacy of chlorambucil plus steroids ($n=9$) versus IV CYC plus steroids ($n=9$), and found that kidney survival was significantly better in the chlorambucil arm. Similar to the former study, the number of patients was small and had impaired kidney function at treatment onset.

A more recent analysis of 32 cases with MN treated with IV CYC (500–750 mg/m² every month for 6 months) plus steroids reported that 81% of the patients achieved CR (13/32) or PR (13/32). Kidney survival was 100% and relapse occurred in five (16%) patients after a median of 16 months after cessation of treatment. The main limitation of this retrospective study was the relatively short follow-up period (30 months) (24). Another current study that compared prospective data of 41 patients treated with IV CYC plus prednisone with a historical cohort of patients who did not receive immunosuppression found that, in the former group, a significantly higher number of patients achieved remission and a more rapid normalization of serum albumin. The median cumulative dose of CYC was 7.2 g and the follow-up period was 2 years. Treatment was well tolerated and few serious adverse events were observed (25).

IV CYC plus steroids has also proved efficacy in attaining immunologic response in a small study from the United Kingdom that included new-incident and relapse patients. Anti-PLA2R levels decreased from 244 U/L to <14 U/L at 6 months. Furthermore, all patients achieved PR at 6 months, despite receiving approximately half the cumulative dose of CYC (4.2–5.4 g) than that of the standard regimen. After a median follow-up of 32 months, 44% of the new-incident patients achieved CR and only two of nine (22%) developed a subsequent relapse (9 and 24 months after initial therapy) (26).

Severe MN with persistent nephrotic syndrome progresses to ESKD in approximately 40%–50% of patients over a period of 10 years (30). In this setting, achieving not only CR but also PR can slow the rate of kidney function decline and has been associated with prolonged kidney survival (30,31). There is general consensus that an effective therapy with a favorable risk-benefit profile is required and there has long been a desire to find a less toxic, but equally effective, therapy than oral CYC (11).

This study must be interpreted within the context of its limitations and strengths. First, it is a retrospective study with an uncontrolled and nonrandomized design. An interesting idea for future prospective randomized trials in MN would be to compare oral versus IV CYC, carefully addressing the efficacy and safety of using lower cumulative doses as in this therapeutic scheme. Secondly, nine patients were lost to follow-up; therefore, information about relapses was not available for the entire cohort. Lastly, we have not been able to describe information related to immunologic remission because serum anti-PLA2R antibody levels were not available in the majority of patients. This must be understood in the context of a historical retrospective analysis in which most patients were diagnosed before the description of PLA2R in 2009.

The main strength of our study is the long follow-up period that allowed us to assess the influence of the therapeutic intervention on kidney survival. The slow-to-form, slower-to-resolve immune deposits (32) suggest that remissions in MN may take years; hence, clinical trials limited to 24 months may not fully describe the true effect on kidney outcomes. We consider that studies based on "real-world experience," as is the case of this work, provide relevant and useful information about uncommon diseases such as MN because they can serve to generate hypotheses. Moreover, we believe the veracity of our data is robust because detailed review of the clinical record of each patient was done and follow-up information was supported by concordance with national coverage databases. To the best of our knowledge, this is the largest cohort of patients with MN treated with IV CYC and, more importantly, with the lowest total cumulative dose.

In conclusion, substitution of oral with low-dose IV CYC in the modified Ponticelli regimen seems to be an effective, safe, and affordable treatment for patients with MN. Prospective controlled trials comparing different doses and routes of CYC in MN are needed to address the better safety and efficacy profile. CYC-based regimens remain a viable option, especially in countries where access to new treatment strategies is not yet universally guaranteed.

Disclosures

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Author Contributions

M. Aunchayna, G. Baldovinos, R. Coitiño, C. González Bedat, J. Santiago, and R. Silvariño were responsible for resources; M. Aunchayna, J. Cabrera, A. Ferreiro, L. Gadola, L. Luzardo, G. Ottati, and O. Noboa were responsible for data curation; G. Baldovinos was responsible for validation; J. Cabrera, H. Caorsi, L. Gadola, F. González-Martínez, G. Ottati, and O. Noboa conceptualized the study; J. Cabrera, H. Caorsi, M. Garau, L. Gadola, F. González-Martínez, L. Luzardo, G. Ottati, O. Noboa, and H. Trujillo were responsible for formal analysis; J. Cabrera, L. Luzardo, and G. Ottati were responsible for investigation; H. Caorsi, L. Gadola, and F. González-Martínez provided supervision; R. Coitiño, C. González Bedat, J. Santiago, and R. Silariño were responsible for visualization; M. Garau, L. Luzardo, and G. Ottati were responsible for methodology; L. Gadola, L. Luzardo, G. Ottati, O. Noboa, and H. Trujillo reviewed and edited the manuscript; L. Luzardo and G. Ottati were responsible for project administration; L. Luzardo, G. Ottati, O. Noboa, and H. Trujillo wrote the original draft; and all authors reviewed the final manuscript.

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