Jacobs Publishers

OPEN ACCESS

Jacobs Journal of Nephrology and Urology

Original Article

Short-Term Outcome of Sub-saharan Africans with Proliferative Lupus Nephritis Treated with Cyclophosphamide Versus Mycophenolate Mofetil

Mbengue M[1], Faye M[1], Lemrabott AT[1], Cissé MM[1], Fall K[1], Keita A[1], Faye M[1], Ba B[1], Diagne S[1], Keita N[1], Ba MA[1], Dieng A[1], Niang A[1], Diouf B[1], Ka EF[1]

[1]Nephrology Department of the Aristide Le Dantec Hospital, Dakar, Senegal.

*Corresponding author: Mansour MBENGUE, Nephrology department of the Aristide Le Dantec Hospital, Dakar, Senegal ; Tel: 00221774443275 ; Email: mansourmbengue92@gmail.com

Received Date: 01-26-2019

Accepted Date: 02-04-2019

Published Date: 02-07-2019

Abstract

Introduction: The proliferative classes are the most frequent in the literature, varying between 40 and 80% of cases. They are indisputably those with the poorest prognosis in the medium term. We conducted this study to evaluate the progression aspects of proliferative lupus nephritis after induction therapy of Sub-saharan Africans patients.

Patients and Method: We performed a retrospective and descriptive study, over a period of 10 years in the nephrology department of Aristide Le Dantec hospital in Dakar. Patients with proliferative lupus nephritis were included.

Results: In a total of 64 black patients with lupus nephritis, there were 44 cases of proliferative glomerulonephritis, a prevalence of 68.7%. The mean age of the patients was 31.8 ± 11.2 years. There were 33 women and 11 men, a sex ratio of 0.3. Hypertension was found in 22 patients. Mean serum creatinine was 24.2 mg / l ± 23.2. Renal failure was present in 45.5% of patients. Mean proteinuria was 3.9 g / 24 ± 2.7. Nephrotic syndrome was found in 72.7% patients. Class III was found in 11.3% of cases, class IV in 27.3%, the association of classes III and V in 43.2% and the association of classes IV and V in 18.2% of cases. Cyclophosphamide was used in 22 patients and mycophenolate mofetil in 10 patients. The rate of remission was higher in patients who were on mycophenolate mofetil than those who were on cyclophosphamide (66.6% versus 36.8%). Death was observed in 5 patients and the causes were pulmonary embolism, bacterial meningitis, pulmonary tuberculosis and indeterminate in 2 patients. End-stage renal disease was found in 8 patients. Infectious complications occurred in 38.6% of patients and cutaneous (32%), uro-genital (24%) and pulmonary (16%) localizations were the most frequent.

Conclusion: The risk of progression to chronic renal failure was relatively high. The remission rate was higher in patients who were on mycophenolate mofetil. The hypothesis of an ethnic participation in the therapeutic response is debatable.

Keywords: Proliferative Lupus Nephritis, Cyclophosphamide, Mycophenolate Mofetil, Remission

Introduction

The proliferative classes are the most frequent in the literature, varying between 40 and 80% of cases [1,2,3]. They are the most severe, often associating a renal insufficiency and a nephrotic syndrome. The induction treatment of these proliferative classes includes corticosteroid therapy, combined with immunosuppressive therapy with cyclophosphamide or mycophenolate mofetil. Although biotherapies have not yet been shown to be effective in this indication, new protocols suggest an improvement in the remission rates achieved after an induction treatment and, possibly, cortisone sparing for patients. They are indisputably those with the poorest prognosis in the medium term [4], especially for the forms associated with an important extra-capillary proliferation or advanced interstitial fibrous lesions. The renal prognosis varies according to the ethnic context (worse in black patients) with a risk of progression to End-stage renal disease that can reach 40 to 60% in the long term.

Patients and Method

We performed a retrospective and descriptive study, over a period of 10 years from 01 January 2007 to 31 December 2016 in the nephrology department of the Aristide Le Dantec Hospital in Dakar. Patients with proliferative lupus nephritis were included. We conducted this study to evaluate the progression aspects of proliferative lupus nephritis after induction therapy of Sub-saharan Africans patients. Nephrotic proteinuria was defined as proteinuria greater than 3g / 24h.

The diagnosis of lupus nephritis was based on a concordant renal biopsy puncture with proteinuria greater than 0.5 g / 24h or active urinary sediment [5]. The proliferative classes were defined by classes III or IV, with or without class V according to the 2003 ISN / RPS classification [5].

For each selected patient, epidemiological, clinical, biological, histological, therapeutic and progression data were studied. The glomerular filtration rate (GFR) was estimated according to the modification of Diet in Renal Disease (MDRD) formula.

Patients received either intravenous cyclophosphamide 1g / m2 / month or mycophenolate mofetil 2g / day. This immunosuppressive treatment was associated with methylprednisone (15 mg / kg /day for 3 days) followed by prednisone relay 1 mg / kg / day. All patients were on hydroxychloroquine.

The patients were followed for 6 months. Partial or complete remission and resistance were defined according to EULAR / ERA / EDTA criteria [6]. Complete remission was defined as proteinuria <0.5g / 24 and normal GFR or not more than 10% of normal.

Partial remission was defined by a decrease in proteinuria of more than 50% and being <3g / 24h and by a normal or near normal GFR (preferably before 6 months but not after 12 months of induction treatment).

-The resistance was defined by:

• a lack of improvement within 3 to 4 months

• or an absence of partial remission after 6 treatment

The collected data were entered into “The sphinx” version 5.1.0.2

Results

In a total of 64 black patients with lupus nephritis, there were 44 cases of proliferative glomerulonephritis, a prevalence of 68.7%. The mean age of the patients was 31.8 ± 11.2 years. There were 33 women (75%) and 11 men (25%), a sex ratio of 0.3. Renal edema was found in 36 patients (81.8%). The mean systolic blood pressure (SBP) was 141 mmHg and the mean diastolic blood pressure (DBP) was 91 mmHg. Hypertension was found in 22 patients. Mean serum creatinine was 24.2 mg / l ± 23.2. Renal failure was present in 20 patients (45.5%). Mean serum albumin was 25.1 mg / l ± 25.4 and mean serum protein was 55.3 mg / l ± 9.07. Mean proteinuria was 3.9 g / 24 ± 2.7. The C3 and CH50 fractions were down in 2 patients and the C4 fraction was normal in all patients. Anti-nuclear antibodies (ANA) were dosed in 8 patients and positive in all patients. Anti-ENA was dosed in 18 patients (4.9%) and was positive in 16 patients. Native anti-DNA antibody was dosed in 16 patients (36.3%) and was positive in 7 cases. Nephrotic syndrome was found in 32 patients (72.7%) and was impure in 25 cases (56.8%). Class III was found in 5 cases (11.3%), class IV in 12 cases (27.3%), the association of classes III

and V in 19 cases (43.2%) and the association of classes IV and V in 8 cases (18.2). In the treatment, cyclophosphamide (CYC) was used in 22 patients and mycophenolate mofetil (MMF) in 10 patients. Of the 44 patients, 35 were followed for 6 months and 9 were lost to follow-up of. Of the patients who were on CYC, 36.8% were in remission (complete and partial) and 63.2% were resistant to treatment. Of the patients who were on MMF, 66.6 % were in remission (complete and partial) and 33.4 % were resistant to treatment (Table 1).

Table 1: Distribution of Patients according to the Therapeutic Protocol and the Evolutionary Modalities

	Cyclophosphamide(n=22)	Mycophenolate mofetil (n=9)
Remission (complete et partial)	36.8%	66.6%
Resistance	63.2%	33.4%

Death was observed in 5 patients and the causes were pulmonary embolism, bacterial meningitis and pulmonary tuberculosis and indeterminate in 2 patients. Chronic renal failure was found in 8 patients (Table 2).

Table 2: The Different Complications Related to the Disease

Complications	Absolute Frequency	Percentages
Chronic renal failure (CRF)	**8**	**66.7**
stage V CRF stage III CRF	5 3	
Thromboembolic	**3**	**25.0**
Inferior vena cava thrombosis Thrombophlebitis	2 1	
Tamponade	**1**	**8.3**
Total	**12**	**100.0**

Infectious complications occurred in 17 (38.6%) patients and cutaneous (32%), urogenital (24%) and pulmonary (16%) localizations were the most frequent (Table 3).

Table 3: The Different Localizations of Infectious Complications

Infectious Complications	Absolute Frequency	Percentages (%)
Pulmonary	**4**	**16**
Pneumopathies Tuberculosis Pulmonary	3 1	
Cutaneous	**8**	**32**
Shingles Facial abscess Furunculosis Erysipelas Cellulitis	4 1 1 1 1	
Digestive	**3**	**12**
Gastroenteritis	3	
Urinary	**3**	**12**
Lower urinary tract infections Pyelonephritis	2 1	
Genitales	**3**	**12**
Vaginitis Genital herpes	2 1	
Osteoarticular	**1**	**4**
Spondylodiscitis	1	
Neurological	**2**	**8**
Bacterial meningitis	2	
Ophtalmological	**1**	**4**
Herpetic keratitis	1	
Total	**25**	**100**

Discussion

In our series, the mean SBP was 141mmgh and the mean DBP was 91mmgh. These results are comparable to those found by Ayodele [7], Korbet [8] and Nossent [9] who respectively found mean SBP/DBP 146/90; 142/88; 135/85. This hypertension is multifactorial; the glomerular lesion of lupus is the basis, it is aggravated by renal failure and corticosteroid therapy [10].

Mean serum creatinine was 24.2 mg/l in our series. This result was similar to the results of Ayodele [7], Okpéchi [11] and Korbet [8] where it was respectively equal to 16; 17

and 19 mg/l. However, Moroni, Nossent and Mok had found lower values which were respectively 11; 10 and 12 mg / l [12, 9, 13]. Mean serum creatinine in our series was similar to studies performed in black patients and was higher than studies in caucasian patients. This could be explained by the more severe nature of lupus nephritis in black patients [14]. In fact, other studies performed in the past showed this severity in black patients of lupus and in particular of lupus nephritis. This is the case of the study conducted by Contraras in the USA and the LUMINA study (Lupus in Minorities, nature vs nurture) which showed a more severe damage in black patients. And this would be associated with the presence of the HLA-DRB1 * 1503 (DR2) group in these patients [14].

In our series, the remission rate (complete and partial) of patients who were on MMF was significantly higher than that of patients who were on CYC (66.6% vs. 36.8%). A large randomized study (ASPREVA) [5] has confirmed that MMF can be used as induction therapy for proliferative lupus nephritis, with a comparable efficacy rate to cyclophosphamide (remission rate of 56% vs. 53%). %). In other series, Chan, Sahay, and Mendoncal [15,16, 17] found a similar initial remission rate in patients who were on CYC and those who were on MMF (Table 4). These studies were conducted in predominantly non-black populations, suggesting ethnicity implication in the difference in therapeutic response to our series.

Table 4: Remission rates Reported by Some Studies according to the Therapeutic Protocol

Authors	Cyclophosphamide	Mycophenolate mofetil
ASPREVA	53	56.2
Mendonca	85.95	88.24
Chan	90	95
Sahay	72.5	72.8
Our series	36.8	66.6

Indeed, a secondary analysis of the ASPREVA study [18] demonstrated a significant impact of interactions between treatment response and ethnicity. CYC remision rate was similar to that of MMF in Asians (53.2 vs. 64.9%, respectively) and caucasian patients (56 vs. 54.2%), but significantly lower than MMF in black patients (40 vs. 53.9%) and Hispanics (38.8 vs. 60.9%). This results suggest an inadequacy of the NIH (National Institutes of Health) protocol that was used in the majority of our patients.

The frequency in the literature of infectious complications varies from 26 to 78% [19]. It was 38.6% in our study. This frequency is comparable to that reported in France (40%) [20], it is greater than that observed in Canada (25%) [21] and India (26.5%) [22]. Infections can reach one or more organs at a time. They affect the lung, skin and urogenital tract in more than two-thirds of cases [23, 24]. In our study, these three locations represented more than 70% of cases. The other localizations (osteoarticular, central nervous system, endocardium ...) were rare.

Lupus predisposes to infectious complications. Indeed, some intrinsic factors are involved in this immunosuppression: decreased chemotaxis and phagocytosis; functional asplenia [25]; hypocomplementemia due to excessive consumption of complement C3 and C4 fractions or congenital deficiency in certain complement fractions (C1r, C1s, C3 and C4) [24]; increased levels of Fc gamma III and GM-CSF, decreased cytotoxic activity of T lymphocytes (CD8) and the production of several factors having a major anti-infectious role (interleukins 1 and 2, interferons ...) [23].

Renal impairment also exposes to infectious complications by the immunosuppression created by chronic kidney failure and hypogammaglobulinemia during nephrotic syndrome.

Other elements are frequently associated with the occurrence of infectious episodes. These are lymphopenia and immunosuppressive treatments [21, 26].

Conclusion

The risk of progression to End-stage renal disease was relatively high. Death was linked to infectious and thromboembolic complications. The remission rate was higher in patients who were on mycophenolate mofetil. The hypothesis of an ethnic participation in the therapeutic response is debatable.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Statement

The local ethics committee approved the study.

Informed Consent

This research involve human participant, they have signed the informed consent.

References

1. Momtaz M, Fayed A, Wadie M et al. Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. Lupus. 2017; 26(14):1564-1570.

2. Moroni G, Radice A, Giammarresi G et al. Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis. 2009; 68: 234–237.

3. Okpechi IG, Swanepoel N, Tiffin N et al. Clinicopathological insights into lupus nephritis in South Africans: a study of 251 patients. Lupus. 2012; 21: 1017–1024.

4. Bujan S, Ordi-Ros J, Paredes J et al. Contribution of the initial features of systemic lupus erythematosus to the clinical evolution and survival of a cohort of Mediterranean patients. Ann Rheum Dis. 2003; 62(9):859-65.

5. Bajema IM, Wilhelmus S, Alpers CE. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018; 93(4):789-96.

6. Barr RG, Seliger S, Appel GB, et al. Prognosis in proliferative lupus nephritis: the role of socio-economic status and race/ethnicity. Nephrol Dial Transplant 2003; 18:2039–46.

7. Ayodele OE, Okpechi IG, Swanepoel CR. Long-term renal outcome and complications in South Africans with proliferative lupus nephritis. Int Urol Nephrol. 2013; 45(5):1289-300.

8. Korbet SM, Lewis EJ, Schwartz MM et al. Factors predictive of outcome in severe lupus nephritis. Am J Kidney Dis. 2000; 35: 904–14.

9. Nossent HC, Koldingsnes W. Long-term efficacy of azathioprine treatement for lupus nephritis. Rheumatology (Oxford). 2000; 39(9): 969-74.

10. Martin-Gomez MA, Frutos Sanz MA, De Ramon Garrido E et al. Malaga Study: 25 Year Background in Lupus Nephritis in South of Spain. Lupus Open Access. 2016; 1:1.

11. Okpechi IG, Swanepoel N, Tiffin N et al. Clinicopathological insights into lupus nephritis in South Africans: a study of 251 patients. Lupus. 2012; 21:1017–1024.

12. Moroni1 G, Quaglini2 S, Gallelli B. The long-term outcome of 93 patients with proliferative lupus nephritis. Nephrol Dial Transplant.2007; 22: 2531–2539.

13. Mok CC, Ying KY, Leung NW. Long-term Outcome of Diffuse Proliferative Lupus Glomerulonephritis Treated with Cyclophosphamide. Am J Med. 2006; 119(4):355.e25-33.

14. Contreras G, Lenz O, Pardo V et al. Outcomes in African Americans and Hispanics with lupus nephritis. Kidney Int. 2006; 69(10):1846-51.

15. Chan TM, Tse KC, Tang CSO et al. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005; 16(4):1076-84.

16. Sahay M, Saivani Y, Ismal K, et al. Mycophenolate versus Cyclophosphamide for Lupus Nephritis. Indian J Nephrol. 2018; 28(1): 35–40.

17. Mendonca1 S, Gupta2 D, Ali S. Mycophenolate Mofetil or Cyclophosphamide in Indian Patients with Lupus Nephritis: Which is better? A Single-Center Experience. Saudi J Kidney Dis Transpl 2017; 28 (5):1069-1077.

18. Isenberg D, Appel GB, Contreras G, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology (Oxford) 2010; 49: 128–140.

19. Zonana-Nacach A, Camargo-Coronel A, Yanez P, et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus 2001; 10: 505–10.

20. Noël V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis 2001; 60: 1141–4.

21. Gladman DD, Hussain F, Ibanez D, et al. The nature and outcome of infection in systemic lupus erythematosus. Lupus 2002; 11: 234–9.

22. Shyam C, Malaviya AN. Infection-related morbidity in systemic lupus erythematosus: a clinico-epidemiological study from northern India. Rheumatol Int 1996; 16:1–3.

23. Barri J, Fessler MD. Infectious diseases in systemic lupus erythematosus: risk factors, management and prophylaxis. Best Pract Res Clin Rheumatol 2002; 16: 281–91.

24. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association European Dialysis and Transplant Association (EULAR/ERA-EDTA)recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012; 71: 1771–82.

25. Neilan BA, Berney SN. Hyposplenism in systemic lupus erythematosus. J Rheumatol 1983; 10:332–4.

26. Bosch X, Guilabert A, Pallarés L, et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. Lupus 2006; 15: 584–9.