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Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy

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Ethics declarations

Conflict of interest

The authors declares that they have no conflict of interest.

Ethical approval

This study was conducted retrospectively from data obtained for clinical purposes and it did not need ethical approval.

Abstract

Background

Patients (pts) with primary Membranous nephropathy (MN) have an autoimmune disease caused by autoantibodies against podocyte antigens and 60-80% of them have antibodies directed against the M-type phospholipase A2 receptor (PLA2R). Immunosuppressive treatment is recommended in high-medium risk pts. Recently the use of rituximab (RTX), has emerged as an important therapeutic option in pts with primary MN. The appropriate cumulative dose of RTX in PMN pts is still uncertain, and favorable outcomes even with low-dose of RTX has been described. We compared efficacy and safety of 3 different treatment regimens: low-dose RTX (Protocol 1, one dose of RTX 375 mg/m2), standard RTX protocol (Protocol 2, four weekly doses of rituximab 375 mg/m2) and Ponticelli's regimen.

Methods

42 pts with primary MN and nephrotic syndrome were assigned to Protocol 1 (14 pts) or Protocol 2 (14 pts). All patients were followed for 24 months after RTX. Fourteen pts, matched for age and baseline serum creatinine (sCr) and proteinuria, treated with Ponticelli's regimen were examined as controls.

Results

At 24 months, a significant improvement in proteinuria levels was observed in pts treated with Protocol 1 (7.5 ± 4.8 at T0; 0.21 ± 0.15 at T24, $p < 0.01$), Protocol 2 (5.1 ± 1.41 g/24 at T0; 0.35 ± 0.39 at T24 $p < 0.01$) and controls (8.27 ± 4.78 T0; 2.2 ± 1.9 g/24 h at T24, $p < 0.01$). No differences in clinical response ($p = 0.53$) was observed comparing the 3 groups.

Conclusions
Our data suggest that the RTX is a promising alternative to Ponticelli's regimen even at low-doses. This makes RTX a cost-effective treatment of primary MN in the short and medium terms.

INTRODUCTION

Membranous nephropathy (MN) is one of the commonest causes of adult nephrotic syndrome [1]. Approximately 80% of pts with primary MN have an autoimmune disease caused by autoantibodies. Most of them have antibodies to podocyte M-type phospholipase A2 receptor (PLA2R). A small percentage of pts have antibodies against thrombospondin type-1 domain- containing 7A [2].

The natural course of MN is variable with more than 20% of pts entering spontaneous remission [3]. Persistent proteinuria is associated with 10-year progression to end-stage kidney disease and an increased risk of mortality [4]. Complete remission of proteinuria is associated with excellent long-term renal survival, but even partial remission results in a favorable long-term outcome [5].

Immunosuppressive regimens including corticosteroids, cytotoxic agents, and calcineurin inhibitors are recommended in both high and medium risk pts. More specifically, KDIGO Clinical Practice Guidelines for Glomerulonephritis, which are based on US clinical experience, emphasize the role of calcineurin inhibitors (cyclosporine or tacrolimus), while the Ponticelli schedule is more widely used in Europe [6].

Immunosuppression requires a careful risk/benefit balance, and many of these agents have a narrow therapeutic window and require close monitoring. Indeed, these therapies may result in adverse events such as infection, myelosuppression, and nephrotoxicity [7].

This has led to the search for alternative therapies.

Animal experiments suggest that B cells may be involved in the pathological process of MN. Starting from this assumption, the use of RTX, a mouse/human IgG1k chimeric monoclonal antibody directed against CD20, has emerged as an important therapeutic option in pts with PMN [8, 9].

Several reports from different groups have shown that approximately 70% of pts with PMN achieve complete or partial remission after RTX administration, which is similar to what has been reported for combination therapy with steroids and alkylating agents and better than calcineurin inhibitors [10].

In one of the longest follow-up studies available, our group showed that RTX achieved 80% remission, including 10% partial remission [11]. This study showed for the first time that response was associated with an increase in Treg cells, what was subsequently confirmed by others [12].

RTX protocols for MN pts vary widely among different centers. Some authors administer four 375 mg/m^2 weekly doses (Lymphoma protocol), while others administer two doses of 1 g two weeks apart (so called Rheumatoid Arthritis protocol).

The efficacy and safety of RTX for the treatment of MN has been evaluated in a randomized controlled trails in which rituximab was non inferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months, and was superior in maintaining proteinuria remission up to 24 months [13]. The efficacy of sequential tacrolimus-rituximab therapy compared with a modified Ponticelli protocol is currently being evaluated the STARMEN trial (NCT01955187, ongoing) [14].

The appropriate dose of RTX to be administrated in MN pts is debated. Controversy exists regarding the efficacy of the so-called low-dose (or single dose) RTX [15,16,17,18,19]. To date, no randomized clinical trials have been carried out to compare the efficacy and safety of low versus standard dose RTX. While the results of a controlled trial comparing the efficacy of RTX with the Ponticelli's schedule are pending (NCT03018535), we report a unique single-center experience comparing 3 different treatment protocols: low dose RTX, standard dose RTX (lymphoma protocol), and Ponticelli's regimen (glucocorticoids and

cyclophospamide) which is still thought, especially in European countries, as the gold standard therapy of MN.

METHODS

W This case–control study was conducted at CMID–Division of Nephrology and Dialysis (ERK-Net member), Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, St. Giovanni Bosco Hospital and University of Turin, Italy.

Patients (pts) enrolled in the study had to meet the following criteria: 1. Primary biopsy-proven MN; 2. > 3 months persistent nephrotic syndrome; 3. no previous immunosuppressive treatment.

All patients have been screened for infections (including HBV and HCV), and complete blood count, chest X-ray and urinalysis were performed before therapy administration. Patients with rapidly progressive renal failure, hepatitis B, diabetes or secondary MN were excluded.

Forty-two patients were examined. Fourteen out of 29 consecutive patients with MN diagnosed between 2014 and 2016 received a single dose of RTX 375 mg/m^2 (Protocol 1) while 15 were excluded due to: non nephrotic proteinuria proteinuria (3 pts), absence of APLA2r antibodies (4 pts), combination of lesions suggestive of secondary MN [4], end stage renal disease (4 pts).

At the time of induction treatment, the clinical database was searched in order to identify the most recent consecutive patients treated with four 375 mg/m^2 weekly doses of RTX (Protocol 2) in the period 2013–2014 or with the Ponticelli's regimen (period 2009–2011), and the patients were matched for age, gender and disease duration at a ratio of 1:1:1. Clinical symptoms, laboratory parameters, outcomes, and complications were collected for the study patients and the control cohorts. Urinary protein excretion and serum creatinine (sCr) were assessed by performing two consecutive 24 h collections at study entry, and at months 3, 6, 9, 12, 18 and 24. All pts treated with Protocols 1 and 2 were positive for Anti-PLA2r antibodies. Pts treated with RTX were also investigated for the CD19 + count in the peripheral blood.

Complete response (CR) was defined as proteinuria ≤0.3 g/24 h, partial response (PR) as sub-nephrotic (≤3.5 g/24 h) proteinuria with >50% reduction of baseline levels, and no response (NR) as <50% proteinuria reduction.

All patients treated with RTX were given premedication with hydrocortisone and paracetamol as previously described [10].

The study was performed according to the rules for the treatment of rare diseases of Piedmont region (North-West Italy), and patients gave informed consent.

Statistical analysis

Data were entered and analyzed using SPSS software version 18.0.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis used Student's t test or Mann–Whitney U test for continuous variables reported as median [Interquartile Range (IQR)], and chi-square test or Fisher's exact test for categorical variables reported as n (%) unless otherwise stated.

We used propensity score methods to account for selection bias. Matching on the propensity score was the primary analytic approach employed [20]. First, each patient's probability of receiving Protocol 1 (propensity score) was derived from a logistic regression model where potential confounders (age, sex, proteinuria and sCr level at admission) were regressed onto the binary outcome of response (any) or no response. Continuous variables were modelled using smoothing cubic splines to allow for departures from linearity [21]. Propensity score matching was then performed using a nearest neighbor, 1-to-1 pair match within 0.2 standard deviations (caliper) of the logit of the propensity score and without replacement [22]. (Thus, in random sequence, a patient in the response was selected and then matched to a patient in the no response group with the closest propensity score, within the defined caliper range.

RESULTS

Baseline demographic characteristics and kidney function were similar in all groups. Specifically, no significant differences were also observed in the responders as regard to age, sex, and proteinuria and sCr level at admission (Table 1).

Proteinuria and sCr levels as assessed at baseline and during a 24 months follow-up are shown in Figs. 1 and 2, respectively.

At 24 months, a significant improvement in proteinuria levels in patients treated with Protocol 1 (7.5 ± 4.8 at T0; 0.21 ± 0.15 at T24, $p < 0.01$), Protocol 2 (5.1 ± 1.41 g/24 at T0; 0.35 ± 0.39 at T24 $p < 0.01$), and Ponticelli's regimen (8.27 ± 4.78 T0; 2.2 ± 1.9 g/24 h at T24, $p < 0.01$) was observed.

When comparing the three protocols, no differences in clinical response were found ($p = 0.53$). Nor were any statistically significant changes in sCr and e-GFR as assessed by the CKD-EPI formula in the three groups either at baseline (Table 1) or during the follow-up. In the RTX group 13 out of 14 pts (92.9%) had a complete response while pt was non-responder (7.1%) at 24th month after therapy. In the rtx group 12 pts had a complete response (85.8%), 1 pt had a partial response (7.1%) and 1 pt had no response (7.1%). In the PP group 12 pts had a complete response (85.8%) and 2 pts (14.2%) were non-responders (Fig. 3). No significant differences in response therapy were observed. The clinical outcome expressed by Kaplan–Meier analysis is shown in Fig. 4.

Adverse events

One patient treated with rtx (Protocol 1) experienced a mild infusion reaction with rash spontaneously resolved after temporary discontinuation of the infusion. Among patients treated with RTX, an infusion reaction with itching, skin rash and scratchy throat that completely disappeared after a low dose of hydrocortisone was observed. Two patients had a urinary tract infection resolved with oral antibiotic cycle. In the group treated with Ponticelli' Protocol, one patient with a history of herpes zoster developed viral reactivation that resolved with oral anti-viral drugs. 1 patient developed a carbohydrate intolerance and another 1 developed a mild leukopenia.

All patients treated with RTX achieved a negative CD19+ count one month after therapy. In rxt treated pts, CD19+ cells reappeared between the third and sixth month after therapy. In the group treated with RTX, the CD19s reappeared between 9 and 12 months.

Anti-PLA2r antibodies disappeared in 3–6 months after therapy in all patients treated with rituximab (Protocol 1 and 2) who achieved a clinical response. In non-responder patients, antibodies persisted throughout the follow-up.

All non responders to the rituximab (Protocol 1 and 2) had levels of immunoglobulins above 800 mg/dL.

No patients relapsed within the 24 month-follow-up. Incidentally, 1 patient who responded to rtx relapsed 32 months after therapy and, 1 pt treated whit Ponticelli's Protocol relapsed after 36. A relapse among the RTX group occurred in 1 patient only 47 months after treatment.

The patient treated with rtx received another single dose of rtx and, again, achieved a complete response. The patient who relapsed after Ponticelli's Protocol was treated with RTX. He achieved a complete response, as well. The patient treated with RTX was successfully re-treated with the same scheme

DISCUSSION

The current therapeutic approaches to MN, the most common cause of nephrotic syndrome in adults, are based on steroids and immunosuppressive drugs, which are not specific and carry the risk of severe toxic effects.

Advances in the knowledge of the pathogenic mechanisms of the disease allowed identification of more specific approaches with a more favorable risk/benefit profile.

During the past decade biologic agents have become a crucial treatment option in immunological diseases, including MN. Rituximab has proven to be effective in MN both as first and as second-line

immunosuppressive therapy in these patients. Initial studies [8,9,10,11] used the conventional Lymphoma protocol (4 weekly doses of 375 mg/m2) or the Rheumatoid Arthritis regimen (1 g given twice two weeks apart). Subsequently, low doses of rituximab have been successfully employed using CD19 count to monitor response [15,16,17].

In the present study we compared the efficacy of low dose of rituximab (single 375 mg/m2 infusion), standard dose of 4 weekly infusions, and Ponticelli's regimen.

It is worth noting that this study has some major limitations. Limitations include its retrospective nature and, due to the relatively low prevalence of MN, the small case samples sizes. Moreover, while all pts treated with anti CD20 regimens (Protocols 1 and 2) were required to be positive for anti-PLA2r antibodies by inclusion criteria to further insure the idiopathic nature of the disease, patients given the Ponticelli's protocol could not be tested due to the unavailability of this biomarker when this scheme was extensively used to treat MN patient. Albeit ancillary in our mind, whether this aspect might have influenced inter-group comparisons is actually unpredictable. Finally, matching cases and controls might have produced biases related to unmeasured and hidden covariates, even though no significant differences were observed in the responders as regard to age, sex, proteinuria and sCr levels at admission.

Taking into account these possible drawbacks, present data suggest that the rituximab regimen could be an even more cost-effective treatment than previously thought. At 24 months, the response rates (complete and partial) were identical among the three groups and similar to other studies (which showed complete plus partial responses ranging between 60–70%) [8, 11]. These results confirm that rituximab is a promising alternative option to the Ponticelli's regimen even if given at a low dose.

A possible reason for the effectiveness of the low dose might be intrinsically related to the condition of nephrotic syndrome which is often associated with substantial hypogammaglobulinemia. Low gammaglobulin concentration is known to be a unique trigger for the activit y of neonatal FcRn receptors (the so-called Brambell receptors) which are widely expressed on reticulo-endothelial cells and determine the IgG recycling in the extracellular space. IgG recovery is inversely related to IgG concentration [24, 25]. As rituximab bioavailability could be influenced by serum IgGs concentration as well, rituximab can be relatively preserved in the interstitial space of patients with nephrotic syndrome with low blood levels of immunoglobulins despite a putative increase in urinary excretion [26].

Several reports, albeit from a single group, showed low-dose rituximab to be effective [15,16,17], though one study reported a remission rate less than 50% and suggested that only pts with normal renal function and low levels of proteinuria were likely to achieve response with low rituximab dose [18]. In our cohort the anti-proteinuric effects were not related to baseline levels of proteinuria, and, unlike other series [18, 19], our patients received rituximab as front-line treatment. This could be relevant to explain the apparent discrepancy between our results and other series [18]. Patients who are refractory to other treatments, as well as relapsing cases, are less likely to respond to any therapy, including rituximab.

As compared to randomized controlled MENTOR study our cohort had definite differences in renal function (better) and percentage of patients with anti-PLA2r antibodies (100 vs 74% in MENTOR study). The therapeutic scheme was also different and so was the control group. Also in GEMRITUX study patients treated with rituximab with anti-PLA2r antibodies were lower (73%, instead of 100%). Consonantly with our study design the effects on proteinuria in GEMRITUX study could be appreciated on the long term.

As compared to Ponticelli's scheme, rituximab regimens appeared to be more cost-effective in the short and medium term despite the higher net cost of the pharmacological agent [29]. The use of a low dose (and the availability of biosimilars) can achieve a further cost reduction [29].

High-quality clinical trials are needed to confirm the efficacy and cost-effectiveness of low doses of rituximab versus either other more widely used rituximab schemes or consolidated experience protocol such as Ponticelli's regimen.

References

1 Fervenza FC, Sethi S, Specks U (2008) Idiopathic membranous nephropathy: diagnosis and treatment. Clin J Am Soc Nephrol 3(3):905–919

2 Bomback AS, Fervenza FC (2018) Membranous nephropathy: approaches to treatment. Am J Nephrol 47(Suppl 1):30–42. https://doi.org/10.1159/000481635

3 Polanco N, Gutiérrez E, Rivera F, Castellanos I, Baltar J, Lorenzo D, Praga M, Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN) (2012) Spontaneous remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment. Nephrol Dial Transplant 27(1):231–234. https://doi.org/10.1093/ndt/gfr285

4 Kanigicherla DA, Short CD, Roberts SA, Hamilton P, Nikam M, Harris S, Brenchley PE, Venning MC (2016) Long-term outcomes of persistent disease and relapse in primary membranous nephropathy. Nephrol Dial Transplant 31(12):2108–2114. https://doi.org/10.1093/ndt/gfv435

5 Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry Group (2004) Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney Int 66(3):1199–1205. https://doi.org/10.1111/j.1523-1755.2004.00873.x

6 Disease K (2012) Improving global outcomes (KDIGO): KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2:139–274

7 Howman A, Chapman TL, Langdon MM, Ferguson C, Adu D, Feehally J, Gaskin GJ, Jayne DR, O'Donoghue D, Boulton-Jones M, Mathieson PW (2013) Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. Lancet 381(9868):744–751. https://doi.org/10.1016/S0140-6736(12)61566-9

8 Bomback AS, Derebail VK, McGregor JG, Kshirsagar AV, Falk RJ, Nachman PH (2009) Rituximab therapy for membranous nephropathy: a systematic review. Clin J Am Soc Nephrol 4:734–744. https://doi.org/10.2215/CJN.05231008

9 Remuzzi G, Chiurchiu C, Abbate M et al (2002) Rituximab for idiopathic membranous nephropathy. Lancet 360(9337):923–924 (Erratum in: Lancet 2002 Dec 21-28;360(9350):2090. https//doi.org/10.1016/S0140-6736(02)11042-7)

10 Xu P, He YD, Yu ZM, Luo K, Xie HY, Zou PM, Gu X, Wang SR, Cai JF, Xu Q, Li H, Li XW (2018) Therapy of rituximab in idiopathic membranous nephropathy with nephrotic syndrome: a systematic review and meta-analysis. Chin Med Sci J 33(1):9–19. https://doi.org/10.24920/21803

11 Roccatello D, Sciascia S, Di Simone D, Solfietti L, Naretto C, Fenoglio R, Baldovino S, Menegatti E (2016) New insights into immune mechanisms underlying response to rituximab in patients with membranous nephropathy: a prospective study and a review of the literature. Autoimmun Rev 15(6):529–538. https://doi.org/10.1016/j.autrev.2016.02.014

12 Rosenzwajg M, Languille E, Debiec H, Hygino J, Dahan K, Simon T, Klatzmann D, Ronco P et al (2017) Kidney Int 92(1):227–237. https://doi.org/10.1016/j.kint.2017.01.01

13 Fervenza FC, Appel GB, Barbour SJ, MENTOR Investigators et al (2019) Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med 381(1):36–46. https://doi.org/10.1056/NEJMoa1814427(Treatment of idiopathic membranous nephropathy (MENTOR). Nephron 130(3):159–168)

14 Rojas-Rivera J, Fernández-Juárez G, Ortiz A, Hofstra J, Gesualdo L, Tesar V, Wetzels J, Segarra A, Egido J, Praga M (2015) A European multicentre and open-label controlled randomized trial to evaluate the efficacy

of sequential treatment with tacrolimus-rituximab versus steroids plus cyclophosphamide in patients with primary membranous nephropathy: the STARMEN study. Clin Kidney J 8(5):503–510. https://doi.org/10.1093/ckj/sfv075

15 Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G (2007) Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2(5):93

16 Ruggenenti P, Cravedi P, Remuzzi G (2009) Rituximab for membranous nephropathy and immune disease: less might be enough. Nat Clin Pract Nephrol 5(2):76–77

17 Bagchi S, Subbiah AK, Bhowmik D, Mahajan S, Yadav RK, Kalaivani M, Singh G, Dinda A, Kumar Agarwal S (2018) Low-dose rituximab therapy in resistant idiopathic membranous nephropathy: single-center experience. Clin Kidney J 11(3):337–341. https://doi.org/10.1093/ckj/sfx105

18 Moroni G, Depetri F, Del Vecchio L, Gallelli B, Raffiotta F, Giglio E, Brunini F, D'Amico M, Longhi S, Radice A, Messa P, Sinico RA (2017) Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. Nephrol Dial Transplant 32(10):1691–1696. https://doi.org/10.1093/ndt/gfw251

19 Seitz-Polski B, Dahan K, Debiec H, Rousseau A, Andreani M, Zaghrini C, Ticchioni M, Rosenthal A, Benzaken S, Bernard G, Lambeau G, Ronco P, Esnault VLM (2009) High-dose rituximab and early remission in pla2r1-related membranous nephropathy. Clin J Am Soc Nephrol 4(8):1173–1182. https://doi.org/10.2215/CJN.11791018

20 Austin PC (2010) The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. Stat Med 29:2137–2148

21 Durrleman S, Simon R (1989) Flexible regression models with cubic splines. Stat Med 8:551–561

22 Austin PC (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 10:150–161

23 Roopenian DC, Akilesh S (2007) FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol 7:715–725. https://doi.org/10.1038/nri215529

24 Kuo TT, Aveson VG (2011) Neonatal Fc receptor and IgG-based therapeutics. MAbs 3:422–430. https://doi.org/10.4161/mabs.3.5.16983

25 Deng R, Meng YG, Hoyte K, Lutman J, Lu Y, Iyer S, DeForge LE, Theil FP, Fielder PJ, Prabhu S (2012) Subcutaneous bioavailability of therapeutic antibodies as a function of FcRn binding affinity in mice. MAbs 4:101–109. https://doi.org/10.4161/mabs.4.1.18543

26 Hamilton P, Kanigicherla D, Venning M, Brenchley P, Meads D (2010) Mayo Nephrology Collaborative Group. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol 5(12):2188–2198. https://doi.org/10.2215/CJN.05080610

27 Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, Jefferson JA, Gipson PE, Rizk DV, Sedor JR, Simon JF, McCarthy ET, Brenchley P, Sethi S, Avila-Casado C, Beanlands H, Lieske JC, Philibert D, Li T, Thomas LF, Green DF, Juncos LA, Beara-Lasic L, Blumenthal SS, Sussman AN, Erickson SB, Hladunewich M, Canetta PA, Hebert LA, Leung N, Radhakrishnan J, Reich HN, Parikh SV, Gipson DS, Lee DK, da Costa BR, Jüni P, Cattran DC, MENTOR Investigators (2019) Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med 381(1):36–46. https://doi.org/10.1056/NEJMoa1814427

28 Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, Michel PA, Mihout F, Dussol B, Matignon M, Mousson C, Simon T, Ronco P, GEMRITUX Study Group (2017) Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. Am Soc Nephrol J 28(1):348–358. https://doi.org/10.1681/ASN.2016040449

29 Hamilton P, Kanigicherla D, Venning M, Brenchley P, Meads D (2018) Rituximab versus the modified Ponticelli regimen in the treatment of primary membranous nephropathy: a health economic model. Nephrol Dial Transplant 33(12):2145–2155. https://doi.org/10.1093/ndt/gfy049

Table 1
Characteristics of patients

	rtx ***(n 14)***	**RTX (*n 14*)**	**PP** ***(n 14)***	**p**
Age (years), mean ± SD, median (range)	64.4 ± 10.8, 66 (35–81)	61.4 ± 11.5, 62 (38–80)	67.1 ± 17.5, 73 (29–86)	0.55
Gender (females) [*n* (%)]	5 (35.7)	5 (35.7)	28.6 (40)	0.72
Baseline serum creatinine (mg/dL), mean ± SD	1.05 ± 0.34	1.06 ± 0.46	1.3 ± 0.9	0.48
CKD-EPI eGFR (mL/min), mean ± SD	68.7 ± 26.6	75.8 ± 29.8	80.8 ± 29	0.66
Baseline urinary protein (g/day), mean ± SD	7.5 ± 4.8	5.1 ± 1.41	8.27 ± 4.78	0.10
Baseline serum albumin (g/dL), mean ± SD	2.5 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.62
Baseline CD19%	9.6 ± 2.8	10.2 ± 2.1	–	–
IgG levels (mg/dL) mean ± SD	542.5 ± 209	820.6 ± 417.5	630.3 ± 279.6	0.14

Figure 1

Trend of proteinuria levels in the 3 groups. RTX rituximab, standard dose; rtx rituximab, low dose; PP Ponticelli Protocol

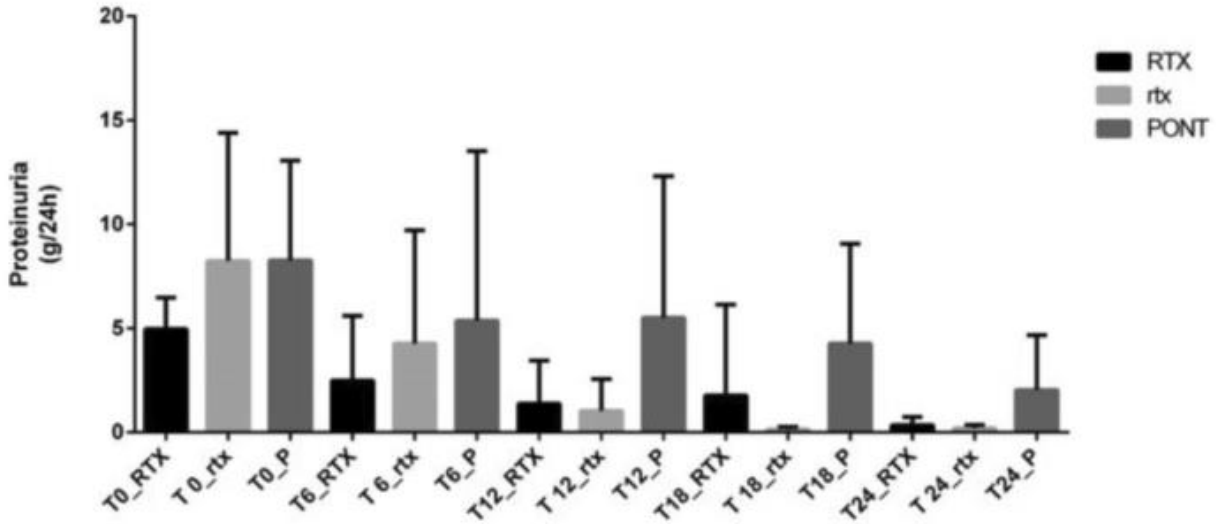


Figure 2

Trend of creatinine levels in the 3 groups. RTX rituximab, standard dose; rtx rituximab, low dose; PP Ponticelli Protocol

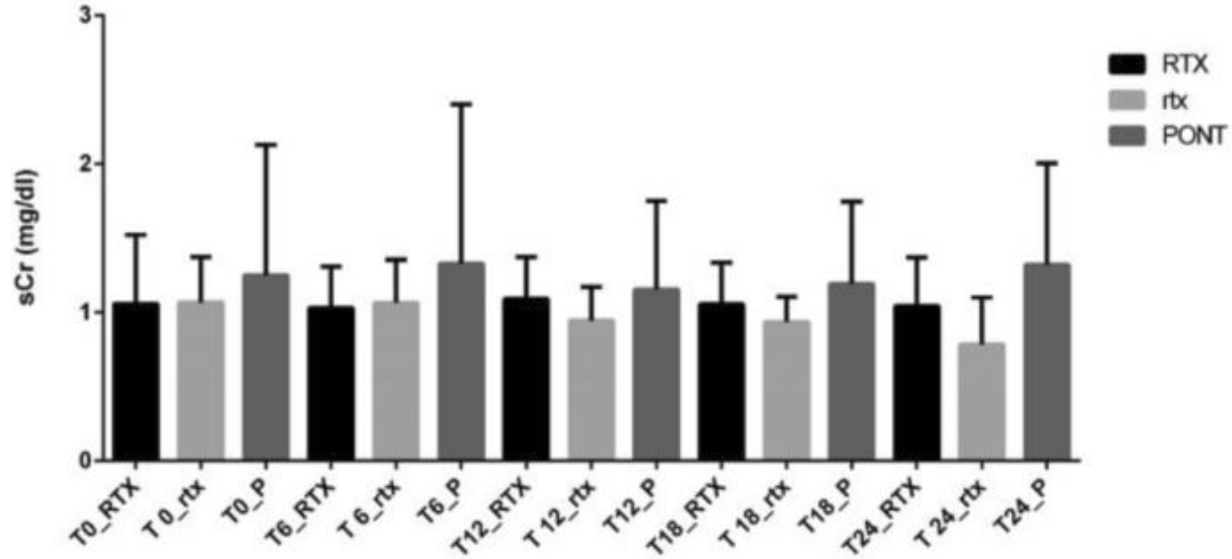


Figure 3

Number of complete response (CR), partial response (PR), no response (NR) in the three groups. RTX rituximab, standard dose; rtx rituximab, low dose; PP Ponticelli Protocol

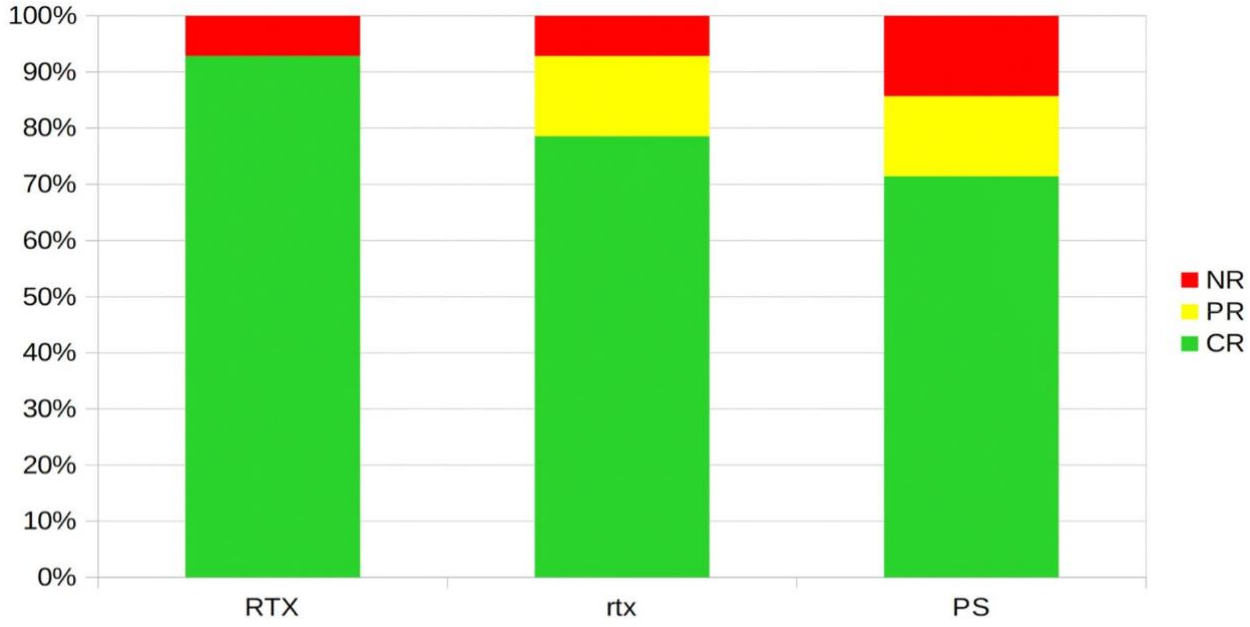
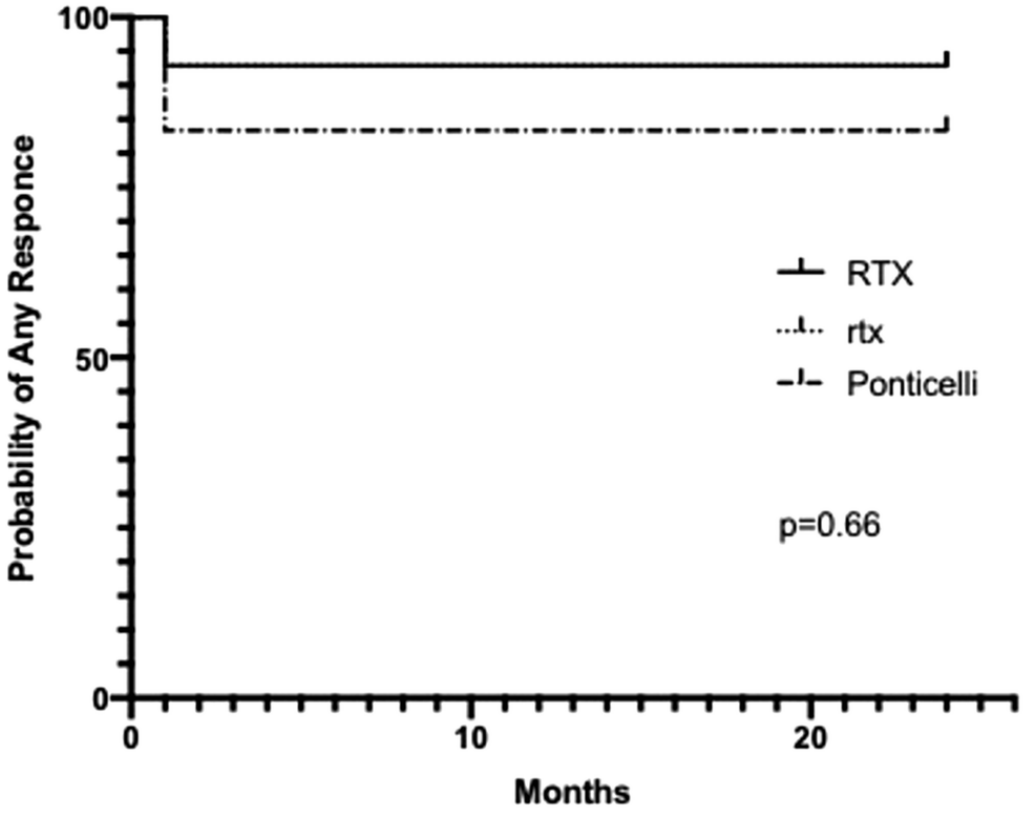


Figure 4

Probability of response represented by Kaplan–Meier analysis. Rtx line and Ponticelli Line overlap