Long-Term Outcomes in Idiopathic Membranous Nephropathy Using a Restrictive Treatment Strategy

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ABSTRACT

Recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend limiting the use of immunosuppressive drugs in idiopathic membranous nephropathy to patients at the highest risk of kidney failure. However, recommendations are based on natural history rather than direct assessment of a restrictive treatment strategy. Here, we describe the long-term outcomes of treating a large cohort of patients with idiopathic membranous nephropathy according to a restrictive treatment policy. We analyzed data for 254 patients who visited our outpatient clinic between 1995 and 2009. All patients were treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Immunosuppressive therapy was recommended in cases of deteriorating renal function or untreatable nephrotic syndrome. Primary outcomes for the present study were renal replacement therapy and death. Secondary outcomes included adverse events during follow-up and remission of proteinuria. In total, 124 patients (49%) received immunosuppressive therapy, which predominantly consisted of cyclophosphamide combined with steroids. Ten-year cumulative incidence rates were 3% for renal replacement therapy and 10% for death. Partial remission rates were 39%, 70%, and 83% after 1, 3, and 5 years, respectively; complete remission rates were 5%, 24%, and 38% at 1, 3, and 5 years, respectively. A serious adverse event occurred in 23% of all patients. The most notable complications were infections (17%), leukopenia (18%), cardiovascular events (13%), and malignancies (8%). In conclusion, the use of a restrictive treatment strategy in this cohort of patients with idiopathic membranous nephropathy yielded favorable outcomes while limiting the number of patients exposed to toxic drugs. These results support current KDIGO guidelines.

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Idiopathic membranous nephropathy (iMN) is the most common cause of adult-onset nephrotic syndrome in whites. Recent data show that iMN is an autoimmune disease, with antibodies against M-type phospholipase A_2 receptor present in about 70% of patients.[1] The natural course of the disease varies, with spontaneous remission occurring in 30%–50% of patients, whereas another 30%–50% show progressive renal failure.[2,3] To avoid progression to ESRD, patients can be treated with immunosuppressive drugs. Two randomized, controlled trials evaluated the efficacy of the alkylating agents chlorambucil and cyclophosphamide.[4,5] These trials included patients with iMN of recent onset, with normal renal function and nephrotic-range proteinuria, and showed increased remission rates and improved renal survival in treated patients. However, outcome was favorable in 60%–65% of the untreated patients. Because most physicians are reluctant to use a treatment schedule that exposes many patients to unneeded, toxic therapy, the use of immunosuppressive therapy in iMN is heavily

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debated. Accordingly, the recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using alkylating agents only in patients at high risk for kidney failure.[6] Thus, in patients with iMN and nephrotic proteinuria, the risk of progression to kidney failure should be balanced against the risks and benefits of immunosuppressive therapy.[7] Unfortunately, few studies have evaluated the safety and effectiveness of a restrictive strategy in patients with iMN. Studies that were performed included small numbers of patients and had a limited follow-up duration.[8–10]

The present study describes the long-term outcome in a large cohort of patients with iMN who were treated according to a restrictive treatment strategy.

RESULTS

Patient Characteristics and Treatment

Patient inclusion is shown in Figure 1. Between 1995 and 2009, 305 patients were evaluated at our center. Fourteen patients were included in a trial and allocated to early treatment,[11] and 17 more were treated before referral. Primary outcomes were all-cause mortality, renal replacement therapy (long-term dialysis or transplantation), and a composite of both. Secondary outcomes were (*1*) severe kidney failure, defined as a serum creatinine level ≥265 μmol/L; (*2*) partial remission of proteinuria, defined as proteinuria <3.5 g/10 mmol creatinine and a decline of ≥50% from baseline combined with a stable serum creatinine; (*3*) complete remission of proteinuria, defined as proteinuria <0.2 g/10 mmol; (*4*) relapse of proteinuria, defined as the recurrence of proteinuria to a level of >3.5 g/10 mmol combined with an increase of ≥50% from the lowest level during remission; and (*5*) adverse medical events during follow-up. Primary outcomes for 20 patients could not be obtained; thus, 254 patients were included in the analyses of outcomes and complications.

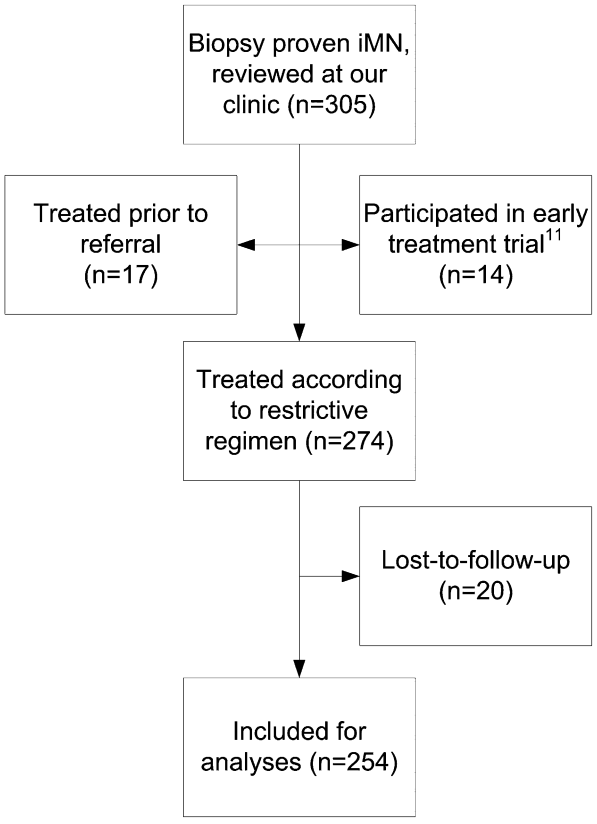

Figure 1. Flowchart showing that 254 of the 274 eligible patients (93%) were included in the study.

Table 1 presents baseline patient characteristics, therapy, and outcome data. Most patients were male, and the mean age ± SD was 53±14 years. Most patients (*n*=226, 89%) had nephrotic syndrome when presenting for urinary analysis, and median estimated GFR (eGFR) according to the four-variable Modification of Diet in Renal Disease equation was 71 (interquartile range, 53–85) ml/min per 1.73 m^2. Patients were followed for a median of 57 months with an interquartile range of 32–90 months. At the time of first referral, 90% of patients used angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and 62% received lipid-lowering medication (statins). During follow-up, ACE inhibitor/ARB use increased to 96%. In addition, 36% of patients used other BP-lowering medication as well. Likewise, statin use increased to 82%, and oral anticoagulants were prescribed to 36% of all patients. In total 124 patients were treated, 77 because of a serum creatinine >135 μmol/L (1.5 mg/dl). These patients had evidence of renal function deterioration, with serum creatinine increasing by ≥25% in all and by >50% in 55 patients. In 47 patients the start of treatment was considered necessary because of persistent deterioration of eGFR of >5 ml/min per 1.73 m^2 per year (*n*=13), persistent severe hypoalbuminemia (serum albumin concentration <20 g/L for 6 months, *n*=13), or complications of the nephrotic syndrome (infections and thrombosis, *n*=6). The rationale for treatment was persistence of the nephrotic syndrome itself in the remaining 15 patients. In total, 91 (36%) patients received combined cyclophosphamide/steroid treatment, whereas 33 (13%) received other immunosuppressive drugs: mycophenolate mofetil (*n*=19), azathioprine (*n*=1), or synthetic adrenocorticotropic hormone (ACTH) (*n*=13). Importantly, 130 patients (51%) received conservative therapy only.

Renal Replacement Therapy and Mortality

The top panel of Figure 2 shows both survival until renal replacement therapy and overall survival. In addition, Table 2 shows cumulative incidence of the primary and secondary outcomes at 1, 3, 5, and 10 years after first referral. In total, seven patients required renal replacement therapy during follow-up, resulting in a cumulative incidence of 3% (95% confidence interval [CI], 1% to 7%) after 10 years. Additionally, the 5- and 10-year mortality rates were 6% (95% CI, 3% to 10%) and 10% (95% CI, 5% to 17%). By comparison, 5- and 10-year mortality rates for the general Dutch population

Table 1. Patient characteristics at baseline and start of immunosuppressive therapy

Variables	Baseline		Immunosuppressive Therapy	
	Total Cohort	Conservative Treatment	Baseline	Start of Therapy
Patients (*n*)	254	130	124	124
Men (%)	68	61	76	
Age (yr)	53±14	51±14	55±13	56±13
Year of biopsy	2003 (1999–2006)	2004 (1999–2006)	2003 (1998–2007)	
Follow-up duration (mo)	57 (32–90)	53 (31–82)	59 (37–103)	
Interval until start of therapy (mo)				4 (1–13)
BMI (kg/m^2)	26.3 (23.8–28.8)	26.0 (23.7–29.0)	26.5 (23.8–28.4)	
eGFR-MDRD4 (ml/min per 1.73 m^2)	71 (53–85)	79 (66–89)	59 (42–73)	41 (31–58)
Serum creatinine (μmol/L)	91 (76–116)	84 (72–94)	109 (86–143)	146 (112–181)
Serum albumin (g/L)	25 (20–29)	28 (23–31)	21 (17–27)	23 (18–27)
Serum cholesterol (mmol/L)	7.2±2.5	6.6±2.1	7.9±2.6	6.8 (5.7–8.4)
Protein-to-creatinine ratio (g/10 mmol)	7.1 (4.6–10.7)	5.1 (3.2–7.7)	10.3 (6.6–12.7)	10.4 (7.1–15.2)
Nephrotic syndrome (%)	89	82	97	
ACE inhibitor/ARB use (%)	90	90	90	
Statin use (%)	62	60	64	
Diuretic use	72	62	83	
Other BP-lowering medication (%)	24	15	33	
Outcomes (%)				
Death	8	4	13	
Renal replacement therapy	3	1	5	
Serum creatinine > 265 μmol/L	11	5	17	
Any partial remission during follow-up	81	79	84	
Any complete remission during follow-up	39	41	37	
Relapses during follow-up (%)				
0	78	84	72	
1	19	14	23	
≥2	4	2	5	

Data are presented as mean ± SD, median (interquartile range), and percentages. BMI, body mass index; eGFR-MDRD4, estimated GFR according to the four-variable Modification of Diet in Renal Disease equation, re-expressed for mass spectrometry traceable serum creatinine concentration; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

with a mean age of 54 years were 3% and 7%.[12] Overall renal survival was 92% (95% CI, 86% to 95%) and 86% (95% CI, 78% to 92%) after 5 and 10 years, respectively. In total, serum creatinine concentration in 26 patients reached values >265 μmol/L, resulting in severe kidney failure incidence rates of 10% (95% CI, 7% to 16%) and 16% (95% CI, 10% to 24%) after 5 years and 10 years. Patients who required immunosuppressive therapy had higher incidences of renal replacement therapy, mortality, and severe kidney failure compared with patients who needed only conservative treatment (Table 2).

Remission and Relapse of Proteinuria

In total, 206 (83%) of 247 patients (7 patients did not have any follow-up laboratory data) showed a remission of proteinuria. As shown in Figure 2 and Table 2, partial remission rates were 39% (95% CI, 33% to 45%), 70% (95% CI, 64% to 76%), and 83% (95% CI, 77% to 87%) at 1, 3, and 5 years. Moreover, 97 of the 206 patients with partial remission improved further and attained a complete remission, resulting in a 10-year cumulative incidence of 52% for complete remission. Half of the patients who achieved a remission were treated supportively, 37% were treated with cyclophosphamide, and the remaining 13% were treated with other immunosuppressive drugs.

A relapse occurred in 46 of the remitting patients, 15 of whom had had a complete remission. Thus, cumulative incidences of relapse were 13% (95% CI, 9% to 19%), 19% (95% CI, 14% to 26%), and 27% (95% CI, 20% to 36%) at 1, 3, and 5 years after remission was first achieved. In total, 25 of the 46 (54%) relapsing patients had reattained a partial remission of proteinuria at the end of follow-up. Notably, three patients who had had a partial but not complete remission progressed to renal replacement therapy.

Severe Kidney Failure

Severe kidney failure, defined as a serum creatinine concentration >265 μmol/L, was observed in 26 patients. Seven of these patients required renal replacement therapy. We analyzed the course of disease in the other 19 patients to ascertain whether these patients had progressive disease and thus would be likely to require renal replacement therapy in the near future. Such patients could be considered to have a poor outcome. The clinical details of these 19 patients and the course of eGFR are illustrated in the table and figures in the Supplemental Material. In summary, 5 of these 19 patients were not treated with any immunosuppressive drugs (2 of the 5 declined to undergo treatment, and 1 was not treated because of severe

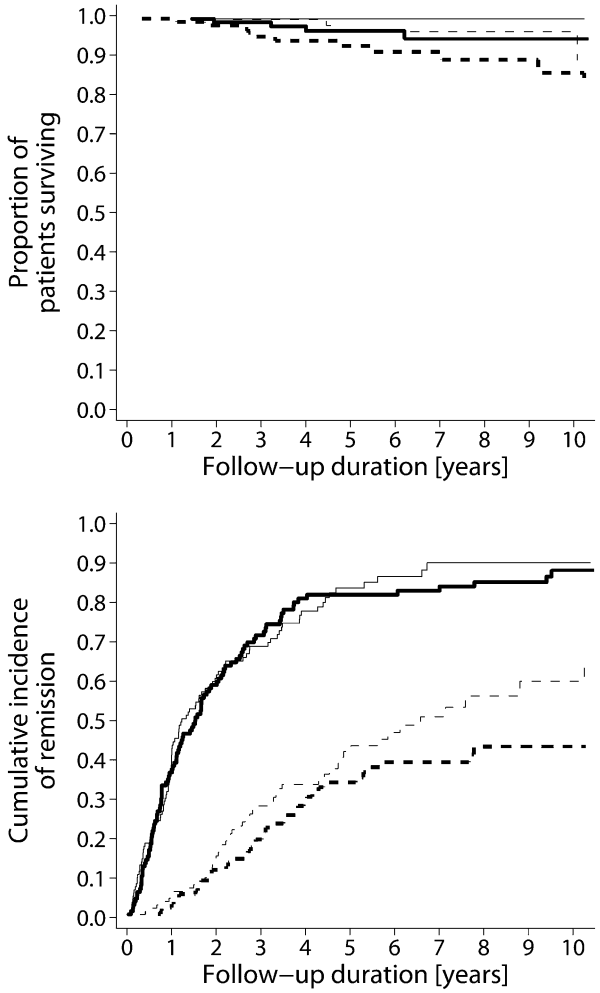

Figure 2. Renal replacement and all-cause mortality rates were higher in the treated patients (top panel). Partial remission rates were similar. However, complete remission rate was lower in the treated patients (bottom panel). The thick lines represent patients treated with immunosuppressive drugs, and the thin lines represent patients treated conservatively. The top panel shows survival until renal replacement therapy (solid lines) and mortality (dotted lines). Death was considered competing for renal replacement therapy in the analyses. The bottom panel shows the cumulative incidence of partial (solid lines) and complete remission (dotted lines). Severe kidney failure was considered competing for remission.

comorbidity). Furthermore, in 9 patients treatment was initiated after the eGFR decreased to <30 ml/min per 1.73 m^2, and in 5 patients treatment was started when the eGFR was still >30 ml/min per 1.73 m^2. Inspection of the individual eGFR curves suggested that progressive disease was present in 9 of the 19 patients who did not go on to renal replacement therapy (see Supplemental Figure 1), 3 of whom were treated with cyclophosphamide, 2 were treated with other immunosuppressive drugs, and 4 were treated conservatively.

KDIGO guidelines recommend that patients with severely decreased kidney function should not be treated because of the elevated risk of complications and unclear efficacy of immunosuppression in these patients. In total, 27 of our patients treated with immunosuppression had an eGFR <30 ml/min per 1.73 m^2 at the start of therapy. Median annual decline in eGFR was 8 ml/min per 1.73 m^2 since baseline. In 19 patients (70%), eGFR stabilized after the start of therapy to an eGFR decline of <1 ml/min per 1.73 m^2 per year over a median follow-up of 5.1 (interquartile range, 2.6–10.8) years from the initiation of treatment onward.

Complications

Overall, 58 patients (23%) sustained a serious adverse event (Table 3). Notable complications were infections (*n*=42, 17%), cardiovascular events (including thrombosis, *n*=33, 13%), and malignancies (*n*=20, 8%). As expected, serious adverse events were more frequent in patients treated with immunosuppression than in those treated conservatively. During follow-up, a malignancy was reported in 20 patients (lung cancer, *n*=5; hematologic malignancy, *n*=5; gastrointestinal cancer, *n*=4; prostate cancer, *n*=2; bladder cancer, *n*=2; renal cell carcinoma, *n*=1; breast cancer, *n*=1). Malignancies occurred more frequently in cyclophosphamide-treated patients.

In total, 21 (8%) patients died, 2 of whom had required renal replacement therapy during follow-up. Furthermore, 8 of the patients who developed a malignancy died during follow-up, 5 as a result of the cancer. Additionally, 4 patients died of cardiovascular causes, and a single patient died following an infection. Unfortunately, cause of death could not be ascertained for the other deceased patients.

Sensitivity Analyses

When patients who received immunosuppressive therapy other than cyclophosphamide were excluded, primary outcome rates as well as partial and complete remission rates remained similar. However, relapse rate was lower at 14%, 20%, and 31% after 3, 5, and 10 years, indicating that relapses occurred more frequently in patients treated with mycophenolate mofetil or ACTH. We also attempted to obtain data on vital status for the 20 patients who were lost to follow-up. Of the 20 patients, 7 had died, and another 7 were still alive; we were unable to ascertain vital status for the final 6. Thus, in a worst-case scenario the estimated 5- and 10-year mortality rates would be 11% (95% CI, 8% to 17%) and 17% (95% CI, 11% to 25%). In addition, none of these 20 patients were registered to have received renal replacement therapy according to the Dutch renal replacement therapy registry (www.renine.nl; Aline Hemke, February 12, 2013, personal communication).

DISCUSSION

Our data support the effectiveness of a restrictive treatment strategy in patients with iMN. With use of this strategy, half of the patients were not exposed to potentially harmful immunosuppressive drugs. Still, long-term outcomes were favorable.

Table 2. Incidence of primary and secondary outcomes

Outcome per Time (yr)	Cumulative Incidence for Total Cohort (95% CI) (*n*=254)	Cumulative Incidence for Supportive Therapy Group (95% CI) (*n*=130)	Cumulative Incidence for Immunosuppressive Therapy Group (95% CI) (*n*=124)
Renal replacement therapy			
1	0 (NA)	0 (NA)	0 (NA)
3	1 (0–4)	1 (0–4)	2 (0–6)
5	3 (1–5)	1 (0–4)	4 (1–9)
10	3 (1–7)	1 (0–4)	6 (2–12)
Mortality			
1	0 (0–2)	0 (NA)	1 (0–4)
3	3 (1–6)	1 (0–5)	5 (2–11)
5	6 (3–10)	4 (1–11)	8 (4–14)
10	10 (5–17)	4 (1–11)	15 (7–25)
Combined			
1	0 (0–3)	0 (NA)	1 (0–6)
3	5 (2–8)	2 (0–7)	7 (4–14)
5	8 (5–14)	5 (2–13)	12 (7–20)
10	14 (8–22)	5 (2–13)	20 (12–33)
Serum creatinine >265 μmol/L			
1	3 (2–6)	0 (NA)	7 (3–13)
3	7 (4–11)	2 (0–7)	12 (7–19)
5	10 (7–16)	4 (2–12)	16 (10–25)
10	16 (10–24)	13 (5–31)	20 (13–30)
Partial remission			
1	39 (33–45)	41 (32–50)	37 (28–45)
3	70 (64–76)	69 (60–76)	72 (63–79)
5	83 (77–87)	84 (75–90)	82 (74–88)
10	90 (85–94)	90 (81–95)	88 (80–93)
Complete remission			
1	5 (2–8)	6 (3–11)	3 (1–8)
3	24 (19–30)	28 (20–37)	20 (13–28)
5	38 (31–45)	42 (32–52)	34 (25–44)
10	52 (44–60)	60 (46–72)	45 (34–56)
Relapse			
1	13 (9–19)	12 (7–21)	14 (8–23)
3	19 (14–26)	14 (8–23)	24 (16–35)
5	27 (20–36)	14 (8–23)	39 (28–52)
10	37 (26–50)	38 (19–65)	39 (28–52)

Renal replacement therapy is the initiation of long-term hemodialysis or peritoneal dialysis or the receipt of a kidney transplant. The combined primary endpoint is a combination of renal replacement therapy and mortality, whichever came first. Partial remission is defined as a 50% reduction in protein-to-creatinine ratio to ≤3.5 g/10 mmol creatinine with a stable serum creatinine. Remission was considered complete when the protein-to-creatinine ratio was <0.2 g/10 mmol. Relapse is the reoccurrence of proteinuria >3.5 g/10 mmol creatinine and a 50% increase from the previous known value of proteinuria in a patient with a remission. CI, confidence interval; NA, not applicable.

Overall renal survival was 86% after 10 years. Furthermore, remission of proteinuria was attained in 83% of all patients. Thus, our data provide evidence for the recommendations in the KDIGO guidelines for the treatment of iMN.

A strength of the study is the standard treatment protocol, which closely resembles that suggested in the recently published KDIGO guideline.[6] In fact, the strategy reported in the present study was even more restrictive than the guideline because treatment was not necessarily started "if proteinuria was over 4 grams per day and remained over 50% of baseline value, and did not show progressive decline during supportive therapy over a period of six months." Therefore, our data suggest that a watchful waiting policy can safely be extended beyond 6 months of follow-up if kidney function is stable and patients do not have severe symptoms from nephrotic syndrome. In addition, clinically relevant long-term endpoints were recorded and the duration of follow-up was sufficiently long for these endpoints to be attained. Moreover, safety of the treatment strategy was evaluated. Finally, surrogate endpoints, such as remission of proteinuria, were also evaluated, thus allowing practitioners to assess effectiveness of the therapeutic regimen in an individual patient at an early stage of follow-up.

Our findings suggest that a substantial number of patients with iMN need only supportive therapy. From this we conclude

Table 3. Adverse events and complications during follow-up

Adverse Event	Cyclophosphamide (*n*=91)	Other Immunosuppression (*n*=33)	Conservative Treatment (*n*=130)
Serious adverse event	35 (38)	11 (33)	12 (9)
Resulting in (prolongation of) hospitalization	13 (14)	3 (9)	2 (2)
Leukopenia	35 (38)	8 (24)	2 (2)
Thrombopenia	7 (8)	2 (6)	0
Liver enzyme abnormalities	7 (8)	0	0
Hyperglycemia	10 (11)	5 (15)	1 (1)
Infection	30 (33)	11 (33)	1 (1)
Hematuria/cystitis	1 (1)	0	0
Cardiovascular/ thrombotic events	18 (20)	7 (21)	8 (6)
Subfertility	0	0	0
Osteonecrosis	0	0	0
Malignancy	14 (15)	2 (6)	4 (3)

Serious adverse events have been defined according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines. Values are *n* (%).

that any future trials that study immunomodulating therapeutic interventions should be restricted to high-risk patients only. Furthermore, this study confirms previous reports that complete remission of proteinuria is a good indicator of a favorable prognosis.[13] In addition, patients who showed severe kidney failure were more likely to progress to renal replacement therapy. However, even in these patients immunosuppressive therapy may still stabilize and even improve kidney function, although compared with patients with preserved kidney function, efficacy may be reduced.

In the recently published KDIGO guidelines for iMN, a restrictive treatment strategy in patients with iMN is recommended.[6] According to these guidelines, initial therapy should be started only if proteinuria is persistently >4 g/d after 6 months of conservative therapy and does not show a tendency to decline; if serum creatinine concentration has risen by >30%; or if severe, disabling, or life-threatening symptoms related to the nephrotic syndrome are present. Although the decision to start treatment was not based on proteinuria in our cohort, the renal function criterion and severity criteria were similar to the guidelines. The KDIGO recommendation was based on studies that included a relatively small number of patients with a limited follow-up duration. Compared with previously published cohorts, the present study included substantially more patients, and patients were, on average, followed for a longer period.[8–10] Nevertheless, both remission and renal survival rates in the present study were similar or even higher. Additionally, the overall renal survival attained in our population was similar to survival in the intervention groups of the trials by Ponticelli *et al.* and Jha *et al.*[4,5] Therefore, our results add to the notion that immunosuppressive therapy should be withheld in patients with well preserved kidney function, despite the (sometimes prolonged) presence of the nephrotic syndrome.[14]

Recently, Howman *et al.* reported the results of a randomized controlled trial that compared chlorambucil and prednisone with cyclosporine monotherapy or conservative treatment.[15] Immunosuppressive therapy was initiated in patients with established deterioration of renal function. Chlorambucil significantly improved renal outcome, thus confirming that late start (or restrictive use) of immunosuppressive therapy is effective. However, because deterioration of kidney function continued in 58% of the chlorambucil-treated patients, this study may question the overall efficacy of restrictive therapy with chlorambucil.

Clearly, outcome in our treated patients was better, and there may be several explanations. Rather than using chlorambucil, we treated patients with cyclophosphamide, which is better tolerated. As a result patients may be more likely to receive an optimally efficacious dose.[16,17] Furthermore, Howman and colleagues' trial provided chlorambucil for 3 months, whereas our patients were treated with cyclophosphamide for 6–12 months continuously. Finally, in the earlier trial, patients had an average creatinine clearance, calculated with the Cockcroft-Gault formula, of 50 ml/min per 1.73 m^2, whereas the mean creatinine clearance by the Cockcroft-Gault formula was 62 ml/min per 1.73 m^2 at the start of treatment in our cohort. In summary, our patients were treated earlier and longer and with a drug that is often better tolerated.

In the present study, 23% of patients sustained a serious adverse event anytime during follow-up. Approximately half of these events were due to infections, and most of these occurred in patients treated with immunosuppressive agents, despite antibiotic prophylaxis.[11] We observed a similar rate of infections and leukopenia compared with other patient populations often treated with cyclophosphamide. Here, the probability of an infection was approximately 20% compared with 15%–60% in patients with lupus nephritis.[18] Similarly, the chance of leukopenia in our patients was 20% compared with 15–50% in those with lupus nephritis. We observed a 13% chance of cardiovascular and thrombotic complications. By comparison, Lionaki *et al.* observed an 8% venous thrombosis risk in patients with iMN.[19] However, their definition of thrombotic events did not include cardiovascular events.

Malignancy is undoubtedly the most feared long-term complication of cyclophosphamide. In our current cohort, malignancy occurred in 20 patients (8%) and was significantly more frequent in patients treated with cyclophosphamide (*n*=14, 15%). Our treatment schedule used from 1995 onward—1.5 mg/kg for 12 months and resulting in a cumulative dose of 36–46 g—was based on the study by Bruns *et al.*[20]

because the Ponticelli regimen had not proven its efficacy in high-risk patients. With the 12-month course of cyclophosphamide, we were able to report good results in high-risk patients who had renal insufficiency.[10] On the basis of the available literature at the time, we considered a cumulative dose <50 g acceptable.[21] Recent data questioned this threshold value and suggested that cumulative doses >36 g should be avoided.[22] Our experience and the results presented in the current study confirm this observation. Therefore, we have recently changed our treatment schedule from 12 to 6 months of cyclophosphamide therapy, halving the cumulative dose.[23] Finally, we observed an overall mortality rate nearly double that in the general population. However, our data compared favorably to the 5-year mortality rate of 6%–26% reported in other iMN cohorts.[8,24,25]

A limitation of the present study is its observational nature. No causal inferences about the efficacy of the strategy or about the efficacy of individual drugs can be made with the current design. Additionally, selection bias is possible because most patients were referred and did not present directly. Patients with an evidently poor prognosis or patients whose disease course is expected to be benign may not have been referred. Furthermore, we were unable to collect complete follow-up data for all patients. However, a sensitivity analysis addressed the potential effect of missing data. Additionally, one may argue that the favorable 10-year outcomes may not adequately reflect survival over longer periods because 26 patients did show severe kidney failure. In a more detailed analysis, we observed 9 progressive patients among the 19 patients who had severe kidney failure but did not require renal replacement therapy. In a worst-case scenario, one would thus expect 16 cases of RRT instead of the 7 we observed, increasing the 10-year cumulative incidence to about 8%. Moreover, the results presented here are valid only for our cyclophosphamide-based strategy. Inferences on other immunosuppressive regimens should be made with caution. Finally, given that risk prediction for patients with iMN has substantially improved throughout the last decade[2,26,27] and patients who do require immunosuppressive treatment may be better off when treatment is started at an early stage, the strategy described here may be improved. On the other hand, no differences in outcome were observed in a trial comparing early versus late initiation of therapy.[11] In other words, the optimal timing of therapy still needs to be elucidated.

In conclusion, a restrictive therapeutic regimen yields favorable long-term outcomes. Additionally, it results in half of the patients not requiring toxic drugs. Short-term and long-term adverse effects remain an important issue, and risks of adverse effects should be balanced against the potential benefits of treatment. Overall, our study supports the recommendations in the recently published KDIGO guideline.

CONCISE METHODS

Patients and Treatment

We included adult patients with biopsy-proven iMN nephropathy who were referred to our clinic between 1995 and 2009. Secondary causes were ruled out per standard policy.[7] Written informed consent was obtained, and the study was performed in accordance with the Declaration of Helsinki. Many patients participated in predictor studies described previously and were treated according to our restrictive strategy.[2,7] Patients who were not treated restrictively, for instance during a clinical trial on the effects of early treatment, were excluded.[11] The strategy is described in detail elsewhere.[7] In summary, patients with serum creatinine concentrations <135 μmol/L (1.5 mg/dl) received supportive treatment. This treatment consisted of BP control and proteinuria reduction with ACE inhibitors or ARBs and further BP-lowering drugs, if needed, to achieve target levels <130/80 mmHg. Additionally, statins were given to treat hypercholesterolemia and anticoagulant therapy was initiated in patients with severe hypoalbuminemia (<20 g/L). In patients with serum creatinine concentrations >135 μmol/L at presentation or during follow-up, immunosuppressive therapy was advised. Severe, debilitating nephrotic syndrome as judged by the treating physician was considered an indication to start treatment with alkylating agents as well. Oral cyclophosphamide (1.5 mg/kg daily for 12 months) and pulse intravenous methylprednisolone (1 g on days 1–3, 61–63, and 121–123) in combination with high-dose oral prednisone (0.5 mg/kg every other day for 5 months before tapering) was the preferred immunosuppressive treatment. Occasionally, other drugs were prescribed as part of a clinical trial or when cyclophosphamide was contraindicated.[11,28] From 1999 onward, trimethoprim-sulfamethoxazole was added to the regimen to prevent *Pneumocystis jiroveci* pneumonia.[11]

Outcomes

Primary outcomes were death, renal replacement therapy (defined as start of long-term dialysis therapy or pre-emptive kidney transplantation), and a combination of both. Renal survival was defined as surviving until renal replacement therapy or mortality, whichever came first. Survival times of patients who did not reach such endpoints were censored at the date of the last follow-up visit.

Secondary outcomes were as follows:

1. Prespecified adverse medical events, including those known or suspected to be associated with immunosuppressive therapy, regardless of the therapeutic regimen that the patient received. These prespecified events were subfertility (the inability to conceive without medical intervention, such as *in vitro* fertilization), osteonecrosis, hemorrhagic cystitis, malignancies, and thromboembolic and cardiovascular events (including stroke, deep venous thrombosis, and pulmonary embolism, fatal and nonfatal myocardial infarction, and interventions for peripheral vascular disease).

2. Severe kidney failure, defined as a serum creatinine concentration of ≥265 μmol/L (3 mg/dl). This concentration was chosen because it represents a doubling of serum creatinine from the level at which start of treatment in high-risk patients was advised, which was 135 μmol/L (1.5 mg/dl).

3. Partial remission of proteinuria was defined as a decline in the protein-to-creatinine ratio of ≥50% since biopsy to a level <3.5 g/10 mmol creatinine with a stable kidney function.

4. Complete remission of proteinuria, defined as a protein-to-creatinine ratio <0.2 g/10 mmol creatinine.

5. Relapse of proteinuria, defined as a protein-to-creatinine ratio >3.5 g/10 mmol creatinine and a 50% increase from the lowest level of proteinuria after remission had occurred.

Data on the primary outcomes and adverse events were obtained from medical records and correspondence. Severe kidney failure, partial remission, complete remission, and relapse of proteinuria were determined using laboratory data collected during routine follow-up. Unfortunately, no follow-up laboratory data were available for seven patients. Therefore these patients were included only in the analyses for the primary outcomes.

The follow-up time was calculated from the date of biopsy until outcome or end of follow-up for all analyses, except for relapse of proteinuria. Patients were considered at risk of a relapse only if remission was achieved and until relapse occurred or until end of follow-up. The time from the first remission until a relapse or the end of follow-up was used for the analysis of relapses.

Statistical Analyses

Baseline data were expressed as proportions, means ± SD, or medians and interquartile range, where appropriate.

Cumulative incidence rates were calculated using Kaplan-Meier estimates. However, because mortality risk may be competing with renal replacement risk, a competing-risks method was used to calculate the cumulative incidence of renal replacement therapy. Similarly, severe kidney failure was deemed competing for the cumulative incidence of both partial and complete remission.

Two sensitivity analyses were performed. First, the main analyses were repeated after excluding patients who initially received immunosuppressive therapy other than cyclophosphamide. Second, to assess the potential influence that lacking outcome data may have had on our results, we attempted to obtain vital status for patients lacking follow-up data. As a worst-case scenario we assumed patients whose status we could not ascertain to be deceased. The date on which we checked vital status was considered the date of death. Subsequently, 5- and 10-year mortality rates were calculated using Kaplan-Meier estimates. Furthermore, we checked whether any of the patients whose outcome could not be obtained were registered to have received renal replacement therapy according to the Dutch renal replacement therapy registry (www.renine.nl; Aline Hemke, February 12, 2013, personal communication).

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DISCLOSURES

None.

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