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Editorial Reviews

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Alkylating agents in membranous nephropathy: efficacy proven beyond doubt

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Introduction

Idiopathic membranous nephropathy (iMN) is one of the most common causes of the nephrotic syndrome in adults. The clinical course of patients with iMN is quite variable. Untreated, ~40–50% of patients with iMN and nephrotic proteinuria will develop end-stage renal disease (ESRD) [1].

According to data of registries in the USA, Europe, and Australia and New Zealand, MN was the cause of ESRD in 0.47–1.71% of patients who started renal replacement therapy in the period 1980–94 [2].

The treatment of iMN is heavily debated. Although several studies have claimed success of immunosuppressive therapy [3–6], a meta-analysis and Cochrane review published in 2004 concluded that there is insufficient evidence of the efficacy of immunosuppressive therapy [7]. The perception that immunosuppressive therapy is of limited benefit is fostered by recent reviews and research articles which explicitly state that the prognosis of membranous nephropathy has hardly improved in recent years with up to 40% of patients reaching ESRD [8–10]. This ongoing debate may lead to therapeutic nihilism. The uncertainty on the use of immunosuppressive therapy in patients with iMN is reflected in our recent study, in which we evaluated by questionnaire the immunosuppressive strategies that had been used in 45 patients with iMN who started renal replacement therapy in the period 2000–05 [11]. The majority of patients (23; 52%) had not received any immunosuppressive therapy, initial immunosuppressive treatment consisted of prednisone monotherapy in seven patients (16%), cyclosporine and prednisone in five patients (11%), cyclophosphamide and prednisone in another five patients (11%), chlorambucil and prednisone in three patients (7%), and azathioprine and prednisone in one patient (2%).

We summarize the evidence that immunosuppressive therapy using alkylating agents is effective in iMN and improves renal survival. We discuss the risks associated with this treatment and touch upon areas of uncertainty. The introduction of new immunosuppressive agents and biologicals has provided hope for effective and safer treatment of patients with iMN. These new agents must be evaluated in randomized trials. Since alkylating agents are proven effective, these agents should be considered the golden standard of therapy and used as comparator drug in such trials.

Why is immunosuppressive therapy in iMN heavily debated?

It is no surprise that immunosuppressive therapy is heavily debated in patients with iMN. Firstly, there are very few randomized trials in patients with iMN, precluding the provision of guidelines with grade A levels of evidence. Secondly, the natural history of iMN is quite variable, and many studies have reported a relatively good outcome in untreated patients [12]. Of note, as discussed elsewhere [1], the favourable outcome in these studies can be explained by the inclusion of patients with non-nephrotic proteinuria. Obviously, patients with non-nephrotic proteinuria have an excellent prognosis and should not be exposed to immunosuppressive therapy. Thirdly, the immunosuppressive agents have serious side effects, and it is quite difficult to balance the risks and benefits [10]. Following the adagium '*primum non nocere*' (first, do no harm), many physicians, when in doubt, will opt to not expose patients to the side effects of immunosuppression.

To obliviate this doubt, it is important to be able to predict outcome in the individual patient with high accuracy. In recent years, we have made considerable progress in this area. Both the use of a model incorporating duration and magnitude of proteinuria and the change in serum creatinine level over a 6-month period, as well as the measurement of urinary low molecular weight proteins, can predict outcome with accuracy of >85% [13–15]. These models allow a more restrictive treatment policy. Obviously, it is impossible to categorize all patients with a model. If a patient cannot with certainty be categorized as high risk, an expectative treatment policy should be advised.

Alkylating agents are effective and have improved prognosis in iMN

The efficacy of alkylating agents was, until recently, only supported by the results of one randomized, controlled clinical trial conducted in Italy [3]. This study recruited patients with recent onset iMN, a nephrotic syndrome and normal renal function. Treatment consisted of chlorambucil, prednisolone and i.v. methylprednisolone for 6 months in an alternating schedule. Treatment increased remission rate and improved renal survival (Table 1). The efficacy of immunosuppressive therapy with an alkylating agent was recently confirmed in a new randomized, controlled trial by Jha *et al.* [16]. These investigators used a similar treatment schedule, but replaced chlorambucil by cyclophosphamide. Study participants had normal renal function. This study provided further evidence that an alkylating agent increased remission rate and improved renal survival (Table 1). Obviously, both trials included patients with normal renal function who are not at highest risk for developing ESRD. Indeed, ~35% of patients were exposed unnecessarily to immunosuppressive therapy (see Table 1: spontaneous remission rate in the untreated controls). Therefore, many authors advise against adopting such a treatment strategy and advocate to restrict treatment to high-risk patients only. Although the efficacy of immunosuppressive therapy in patients with established renal insufficiency is not proven in randomized trials, two recent cohort studies provided strong support for the efficacy of alkylating agents in these high-risk patients [4,5]. In these studies by Torres *et al*. and du Buf *et al*., a historical control group was used for comparison. Both studies showed better renal survival in the treated patients. Table 1 summarizes the results of the above-mentioned studies, all with a high level of evidence and clinical significant end points (dialysis-free survival).

The efficacy of a restrictive treatment policy (i.e. treating only patients with established renal insufficiency) was demonstrated in another study by du Buf *et al*., who evaluated outcome in a cohort of patients with iMN and a nephrotic syndrome [17]. All patients diagnosed with iMN in the study period were identified by using the central pathology registry, thus excluding any selection bias. In the study period, a restrictive treatment policy was advised, thus limiting immunosuppressive therapy to patients with renal insufficiency or patients with a severe, longstanding nephrotic syndrome. During an average follow-up of 66 months, 22 of 60 patients developed a spontaneous remission. Overall, 33 patients (48%) received immunosuppressive therapy, which consisted of the combination of an alkylating agent and prednisone in 28 patients. Patient survival after 7 years was 100% and renal survival 88%. This study thus indicates that a restrictive treatment strategy which avoids unnecessary exposure to alkylating agents in approximately half of the patients results in a favourable prognosis in patients with iMN. We recently provided additional evidence that the use of a restrictive treatment strategy and cyclophosphamide as alkylating agent alters outcome in patients with iMN. In an epidemiological study, we analysed the incidence of ESRD in the Netherlands and observed that the incidence of ESRD due to

Table 1. Alkylating agents in membranous nephropathy: results of randomized and non-randomized clinical trials

		Patients (no.)	Sex (male/female)	Duration ther. (months)	sCreat (umol/l)	Proteinuria (g/day)	Follow-up (months)	Remission rate (%)[a]	Relapse rate (%)[b]	End points	Level of evidence
RCT	Ponticelli *et al.*1995 [3]										A2
	Supportive therapy	39	29/10	–	93 ± 25	5.3 ± 2.8	120	38	13	Dialysis-free 10-year survival: 60%	
	ChlA/steroids	42	34/8	6	94 ± 22	6.2 ± 3.0	120	83	26	Dialysis-free 10-year survival: 92%	
	Jha *et al.* 2007 [16]										A2
	Supportive therapy	46	27/19	–	103 ± 19	5.9 ± 2.2	132 (126–144)	35	25	Dialysis-free 10-year survival: 65%	
	CP/steroids	47	30/17	6	108 ± 27	6.1 ± 2.5	132 (126–144)	72	24	Dialysis-free 10-year survival: 89%	
Non-RCT	Torres *et al.* 2002 [4]										B
	Supportive therapy	20	15/5	–	124 ± 88	6.9 ± 3.1	47 ± 38	0	–	Dialysis-free 7-year survival: 20%	
	ChlA/steroids	19	11/8	6	124 ± 62	8.9 ± 3.6	52 ± 37	42	25	Dialysis-free 7-year survival: 90%	
	du Buf *et al.* 2004 [5]										B
	Supportive therapy^	24	20/4	–	173 (137–360)	8.5 (0.0–19.6)#	48 (12–185)	20	50	Dialysis-free 5-year survival: 32%	
	CP/steroids	65	55/10	12	171 (106–512)	10.0 (2.0–23.0)#	51 (5–132)	86	20	Dialysis-free 5-year survival: 86%	

Studies of Ponticelli *et al.* and Jha *et al.* were randomized controlled trials in patients with well-preserved renal function. Studies of Torres *et al.* and du Buf *et al.* were observational cohort studies in patients with established renal insufficiency. Data are presented as number, mean ± SD or median (range).RCT = randomized controlled trial; Non-RCT = non-randomized controlled trial; Duration ther. = duration of immunosuppressive treatment; sCreat = serum creatinine; – = not applicable; ^ = unpublished data; # = proteinuria in grams per 10 mmol creatinine; ChlA = chlorambucil; CP = cyclophosphamide.

[a]Definitions of remission as used by the authors.

[b]Relapse rate: percentage of relapses in patients with previous remission.

iMN decreased in our region by 75% when comparing the period 1991–95 with the period 2000–05 [11]. By contrast, the incidence of ESRD due to iMN had remained unchanged in other parts of the Netherlands. Only 18% of patients with ESRD due to iMN had received treatment with an alkylating agent.

With regard to the choice of the best alkylating agent, a comparative study between chlorambucil and cyclophosphamide was performed by Ponticelli *et al.* [18]. In this study, both agents were equally effective in inducing a remission of proteinuria. In our hands, a chlorambucil-based regimen was less effective and more toxic than a regimen based on cyclophosphamide [19]. An overview of studies performed in patients with iMN and renal insufficiency treated with either chlorambucil or cyclophosphamide points towards better efficacy of cyclophosphamide [1]. Moreover, the data suggest that the use of chlorambucil is associated with more side effects (see below).

In conclusion, there is now grade A evidence that alkylating agents are effective in patients with iMN. Additional data strongly suggest that treatment can be restricted to high-risk patients and that a restrictive treatment strategy carries a good prognosis and improves outcome.

Side effects of alkylating agents

Obviously, alkylating agents are toxic drugs. The short-term side effects of both chlorambucil and cyclophosphamide include anaemia, leucocytopaenia, thrombocytopaenia, anorexia, nausea, liver test abnormalities, interstitial pneumonitis and sterile cystitis. Macroscopic haematuria and haemorrhagic cystitis are mainly associated with the use of cyclophosphamide. As discussed elsewhere, chlorambucil is associated with more side effects than cyclophosphamide [5,19]. The magnitude and relevance of these side effects in daily clinical practice can be estimated from the adverse events reported in recent clinical trials in patients with iMN. Ponticelli *et al.* reported side effects in 29% of patients treated with chlorambucil, most commonly gastrointestinal problems, including peptic ulcers [3]. Ten percent of treated patients had to stop therapy because of side effects, and all patients recovered after adequate therapeutic measures. In the study of Torres *et al.*, side effects were observed in 47% of the chlorambucil treated patients, most accounted for by infections (32%) [4]. Jha *et al.* reported infections as the most frequent side effects in both the group with supportive treatment and the patients treated with cyclophosphamide [16]. In this latter group, infections were present in 15% of patients. We ourselves noted haematological abnormalities in more than half of the patients treated with cyclophosphamide, infections in 26%, anorexia and nausea in 12%, and liver dysfunction in 3% [5]. In 46% of patients, the dose was reduced, and in 6% of patients, treatment was prematurely stopped. Although cumbersome, these short-term side effects can mostly be managed by dose reduction, temporary withdrawal of the alkylating agent and appropriate antibiotic therapy. Of note, we currently use cotrimoxazole as standard prophylaxis against pneumocystis jiroveci pneumonia.

The most important and most feared side effects of chlorambucil and cyclophosphamide are infertility and malignancy. Most data are available on the effects of cyclophosphamide. Azoöspaermia may occur when cyclophosphamide is used in a dose of 2 mg/kg/day for >12 weeks in men [20]. In women, the risk of amenorrhoea increases when the cumulative dose of cyclophosphamide exceeds 10–15 g. The risk of amenorrhoea is dependent on the cumulative dose, but also on the age of the patient [20,21]. Thus, in patients with planned parenthood in the future, duration of cyclophosphamide treatment should be limited to 3 months.

Obviously, the most dreaded side effect of cyclophosphamide treatment is the development of malignancies. Recent studies have reported a doubling of the standardized incidence ratio (SIR) of malignancies in patients treated with cyclophosphamide [22,23]. The increased incidence was predominantly attributable to the occurrence of skin cancer (SIR for squamous skin cancer 7.3–11.5), bladder cancer (SIR 3.6–4.8) and leukaemia (SIR 5.7–59).

The late effects of cyclophosphamide have been studied in patients with rheumatoid arthritis and in patients with vasculitis [22,24–26]. The cumulative incidence of bladder cancer was reported to be 4% to 15% at 15 years after drug exposure. The average latency time was 108 months. There is a clear dose dependency, and older studies indicated that bladder cancer occurred in patients who had used >50 g of cyclophosphamide. Median cumulative dose of cyclophosphamide was 113 g in the patients with bladder cancer. Based on these criteria, treatment with cyclophosphamide, 1.5 mg/kg/day for 12 months (cumulative dose 35–40 g), was considered safe until recently.

In two recent studies, the threshold value of 50 g was questioned [23,27]. Travis *et al*. studied the risk of bladder and kidney cancer following cyclophosphamide treatment in survivors of non-Hodgkin's lymphoma [27]. There was no increased risk for malignancies in patients who received a cumulative dose of cyclophosphamide of <20 g. With higher doses, an increased risk was observed; respectively a 6-fold [confidence interval (CI) 1.3–29] and 14.5-fold (CI 2.3–94) increased risk of bladder cancer following cumulative doses of cyclophosphamide of 20–49 and 50 g or more, respectively. However, the contribution of radiotherapy to the increased risk could not completely be excluded for patients receiving 20–49 g. In the second study, Faurschou *et al*. observed a significantly increased malignancy risk in patients who had received >36 g of cyclophosphamide [23]. Interpretation of these data is difficult, since many patients were treated with other immunosuppressive drugs during follow-up. In fact, the SIR of bladder cancer was markedly increased in patients who had received cyclophosphamide and methotrexate (SIR 13.8; 95% CI 2.8–40), and non-significantly higher in patients who had used cyclophosphamide monotherapy (SIR 3.0; 95% CI 0.4–10.8).

Thus, there is no doubt that prolonged use of cyclophosphamide predisposes to the development of a malignancy. Patients must be well informed. However, the risks must not be overrated. Firstly, the actual risk of developing a malignancy is not very high. Secondly, it is unclear if the increased risk is merely dependent or fully attributable to the use of the alkylating agent. It has been suggested that conditions, such as Wegener's granulomatosis, are asso-

ciated with a higher cancer rate, independent from therapy, indicating a possible carcinogenic effect of the disease process itself [26]. Likewise, a recent Norwegian study showed increased incidence of malignancies in patients with iMN, independent of the use of immunosuppressive agents [28]. Thirdly, we must realize that untreated patients are more likely to develop ESRD. Renal replacement therapy is associated with increased mortality due to cardiovascular disease [29–33]. Moreover, renal transplantation, the preferred method of renal replacement therapy in patients aged <70 years, carries a significantly increased risk of malignant disease, due to lifelong treatment with immunosuppressive agents [34–36]. Next to the well known up to 20-fold increased risks of non-melanoma skin cancers and virus-associated cancers, a 2-fold increase in common tumours, including colon, lung, breast, prostate, oesophagus and pancreas, is reported in kidney transplant recipients [34].

Areas of uncertainty

- Based on the available evidence, we can conclude that alkylating agents are effective in patients with iMN. Cyclophosphamide seems to be preferable over chlorambucil, based on data on efficacy and toxicity. Treatment should be restricted to high-risk patients who can be identified by the level and/or the composition of urinary proteins. Several unanswered questions remain. The optimal dose and duration of therapy with cyclophosphamide is uncertain. We have used cyclophosphamide 1.5–2 mg/kg/day for 12 months (cumulative dose 35 g) in high-risk patients and reported a favourable outcome [5,37]. However, in light of recent literature, this relatively high cumulative dose should be questioned. Since a cumulative dose up to 20 g appears to be safe, a treatment period of 6 months could be an alternative. Recent studies of Jha *et al*. and Ponticelli *et al*. showed benefit of treatment with a schedule that included cyclophosphamide in a dose of 2 mg/kg/day for a total of 3 months (cumulative dose ~13 g for a 70-kg patient) [3,16,38]. These latter studies suggest that the dose and duration of cyclophosphamide treatment may be further limited, although it must be realized that the efficacy of these treatment regimens have not been demonstrated when restricted to high-risk patients. A recent study suggested that even lower doses of cyclophosphamide could be used with success [39]. In this study conducted in Asia, all patients with iMN and a nephrotic syndrome were treated with prednisone (30 mg/day with tapering and withdrawal by 2 years) and cyclophosphamide in a dose of 1 mg/kg/day for 3 months, followed by 0.5 mg/kg/day for another 3 months (cumulative dose ~9 g). The authors reported a cumulative incidence of remission of 94% after 8 years. However, the data do not support the conclusion that such a low-dose cyclophosphamide therapy is effective. Firstly, the study population consisted of all nephrotic patients with iMN, with almost 50% females, and well-preserved renal function. Without immunosuppressive therapy, >50% of patients would have developed a spontaneous remission. Moreover, 38% of patients needed a second course of therapy because of initial treatment failure or relapse. Thus, it is likely that the high-risk patients actually received a total dose of cyclophosphamide of almost 20 g.
- Treatment with alkylating agents is usually combined with high-dose steroid treatment. The dose and duration of steroid treatment varies, and clinical trials are lacking. Some authors report a benefit of intravenous methylprednisolone pulses over oral medication [40]. Our steroid regimen consists of methylprednisolone 1 g intravenously on Days 1, 2, 3, 60, 61, 62, 120, 121 and 122, and oral prednisone 0.5 mg/kg body weight every other day for 6 months, subsequently tapered by decreasing the dose with 5 mg/week. Obviously, this treatment is accompanied by the well-known steroid side effects, including cushingoid appearance, hyperglycaemia and osteoporosis.
- The optimal timing of start of therapy is uncertain. Is it better to start early immunosuppressive therapy in high-risk patients or can we wait until renal function deteriorates? Recently, we have conducted a randomized open label trial in patients with iMN and a high risk for progression [41]. Patients started with cyclophosphamide and prednisone immediately after randomization or when renal function deteriorated. In these high-risk patients, the treatment regimen was effective in inducing a remission (>90%) in both treatment arms. Although early treatment resulted in a more rapid onset of remission and therefore shortened the duration of the nephrotic phase, it did not result in a better preservation of renal function at the end of follow-up. It therefore seems that treatment can safely be postponed until renal function deteriorates. However, when postponing treatment, there might be a larger risk of both nephrotic syndrome-related and treatment-related side effects. We suggest that decisions on the timing of start of therapy must be based on an individualized assessment of risks and benefits [41]. The risks of prolonged nephrotic syndrome, i.e. thromboembolic and infectious complications, will favour early start of treatment in patients with a past history of thrombosis, cardiovascular disease and infections, especially in case of severe hypoalbuminaemia. On the other hand, the risk of treatment-related complications, i.e. infertility, infections and steroid-associated side effects, favours late start of treatment in patients with planned parenthood, a past history of diabetes mellitus, osteoporosis or respiratory infections. Finally, age must be taken into account. Elderly patients are more prone to develop treatment-related complications, whereas the likelihood to develop ESRD during lifetime is often small. Some clinical examples are illustrated in Table 2. When risk assessment leads to the decision not to start treatment in an individual patient, re-evaluation should take place after 6 months or earlier if the clinical condition of the patients changes.
- Are there suitable alternatives? Many other therapeutic agents are available in daily clinical practice, i.e. calcineurin inhibitors, mycophenolate mofetil, synthetic adrenocorticotropic hormone (ACTH) and rituximab. An extensive discussion of their efficacy and safety is beyond the scope of this manuscript. Recent studies

Table 2. Treatment decisions in clinical practice: some examples of balancing risks and benefits

	Patient 1	Patient 2	Patient 3	Patient 4
Characteristics				
Age	25	25	65	65
Offspring	None	2	2	2
Medical history	None	2 × DVT	Diabetes, COPD	Myocardial infarction
sCreatinine (umol/l)	90	110	110	180
sAlbumin (g/l)	17	17	21	21
Proteinuria (g/day)	17	17	17	17
β2m- and IgG excretion[a]	↑↑	↑↑	↑↑	↑↑
Considerations				
Favours treatment	• High risk of progression • Nephrotic syndrome	• High risk of thromboembolic complications • High risk of progression • eGFR below normal	• High risk of progression	• Sustained renal function loss • High risk of thromboembolic complications • High risk of progression
Against treatment	• Risk of infertility • Side effects • Normal renal function	• Risk of infertility • Side effects	• Risk of steroid-induced hyperglycaemia • Risk of respiratory infections • Side effects with elder age	• Side effects with elder age
Advise				
	• Supportive treatment	• Start immunosuppressive treatment	• Supportive treatment	• Start immunosuppressive treatment
	• Re-evaluation at 3, 6 and 12 months • Start treatment if sCreatinine increases >25%		• Re-evaluation at 3, 6 and 12 months • Start treatment if sCreatinine increases >25%	

DVT = deep venous thrombosis; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate.
[a]β2m- and IgG excretion: urinary beta-2-microglobulin excretion and urinary IgG excretion. These are considered elevated when, respectively, >500 ng/min and >250 mg/24 hours. Combined elevated β2m- and IgG excretion is a marker of high risk for progression to renal failure.

with these newer agents in patients with iMN have raised optimism on their efficacy, as indicated by high remission rates. However, follow-up was short in most studies, and there are virtually no studies with hard renal end points such as ESRD or 50% decrease of GFR. Long-term randomized controlled trials (RCTs) are needed. We recommend that alkylating agents be considered as comparator drugs in such trials. iMN is a treatable disease in most patients. We should focus on the questions on whom to treat, when to start therapy, and the best sequence of the use of the various immunosuppressive drugs.

Conclusion

In patients with iMN, alkylating agents increase remission rate and improve renal survival. Thus, alkylating agents should be considered the golden standard of therapy. Treatment harbours the risk of severe toxicity. Therefore, cyclophosphamide should only be given to high-risk patients. If possible, a cumulative dose of >20 g should be avoided. Alternative agents with fewer side effects are urgently needed. Still, the efficacy of newer immunosuppressants must be proven on renal end points. In randomized controlled trials evaluating the efficacy of these agents, alkylating agents must be used as comparator drugs.

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Managing hypertension using home blood pressure monitoring among haemodialysis patients—a call to action

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Over the last hundred years, the diagnosis of hypertension has rested upon the indirect measurement of blood pressure (BP) through the auscultation of Korotkoff sounds. Among patients on haemodialysis, BP measurement is particularly important because disparate outcomes are obtained depending on the timing, location, frequency and technique of measurement of BP [1]. This disparity of outcomes has profound implications for the management of hypertension especially among haemodialysis patients. Why home BP monitoring should become the standard of care among patients on haemodialysis is the subject of this review.

To compare tests, such as one that tests home BP to predialysis BP, a diagnostic test study must be performed. A diagnostic test study can have one of the following four paradigms (Figure 1):

(1) Test A (e.g. home BP) is compared to test B (e.g. predialysis BP) using a 'gold-standard' or reference test. If test A performs better than test B, then test A is preferred. Whether test A should be favoured over test B depends on a variety of considerations such as its cost, practicality, invasiveness and acceptability.
(2) The two tests may be compared not to a reference standard but to some intermediate end point. A valid intermediate end point among hypertensive patients is the presence of target organ damage such as left ventricular hypertrophy. In other words, home BP can be compared to pre- or post-dialysis BP and the results compared in their ability to predict echocardiographic left ventricular hypertrophy. If home BP measurement is more strongly related to target organ damage then, compared to paradigm 1, it provides a higher level of evidence that it is superior to pre-dialysis or post-dialysis BP.
(3) The two tests can be compared with respect to prognosis, for example, all-cause mortality. For example, with respect to outcomes such as all-cause mortality, dialy-