Balancing Cancer Risk and Efficacy of Using Cyclophosphamide to Treat Idiopathic Membranous Nephropathy

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In 1950, Coons and Kaplan described a technique for labeling antibodies with fluorescent probes to detect antigens in tissue (1). Using this technique, it was possible to classify glomerulonephropathies according to their appearance by immunofluorescence staining. One distinct entity, membranous nephropathy (MN), was highly characterized by granular deposits of IgG and, frequently, C3 along the glomerular basement membrane (GBM). An identical pattern was reported by Heymann et al. in a rat model induced by immunizing animals with kidney extracts (2). Because the appearance of these deposits was similar to those in experimental animal models of serum sickness induced by circulating immune complexes, it was assumed that MN was an immune complex disease with circulating complexes deposited in GBM with consequent damage. However, work by Couser et al. and Van Damme et al. demonstrated that, instead of being consequent to circulating immune complexes, GBM were indeed bound antigens to which circulating antibodies fixed (3,4).

Studies in humans showed that patients with MN did not have antibodies circulating to the pathogenic antigen in rats, and that some had complexes while others did not. Those that had circulating complexes generally had a systemic illness, such as cancer (5). Over the years the search for target antigens and pathogenic mechanisms in MN has spurred many investigations. Isolated cases of MN with identified GBM antigens were reported but the seminal studies of Beck et al., for the first time, clearly identified one of the major GBM bound antigens against which autoantibodies formed (6). They showed that the majority of patients with idiopathic membranous nephropathy (IMN) (60%–80%), not associated with a systemic disease, had antibodies directed to the M-type phospholipase A2 receptor. Furthermore, antibody titers seemed to reflect treatment (7,8). These important observations have led to a great acceleration of studies to clarify the pathogenic mechanisms of IMN so that appropriate, specific therapy can be tailored.

In the meantime, the quest for treatment for this enigmatic, sometimes devastating disease has led to numerous empirical interventions. Early noncontrolled trials suggested a beneficial effect of prednisone, but the randomized Boston Collaborative Study was unable to confirm this effect (9). Following this, a variety of immunosuppressive strategies have been explored in IMN patients with underlying renal insufficiency at high risk of progression to ESRD. Two large controlled trials demonstrated improved renal survival with alkylating agents in combination with steroids (10,11). Additionally, cohort studies confirmed the benefits of cytotoxic therapies, with cyclophosphamide being the preferred agent (12–14). A recently published meta-analysis revealed significant reduction in ESRD in response to combined alkylating agent and corticosteroid therapy (15). Overall, in studies with alkylating agents, 5-year renal survival is 86%–92%, remission rates range from 64% to 85%, and relapse rate is 25% after 5 years (16).

Additional therapeutic options include calcineurin inhibitors, mycophenolate (MMF), rituximab, and adrenocorticotropic hormone (ACTH). Of the above, calcineurin inhibitors (cyclosporine and tacrolimus) are successfully used in treating IMN (17–19). Cumulative data indicate that calcineurin inhibitors are effective in inducing remission of proteinuria in ≤80% of patients (18,20). In addition, calcineurin inhibitors have produced favorable responses in patients unresponsive to other immunosuppressives (20,21). However, 50%–72% of patients have been shown to relapse after stopping treatment (18,20,22) and may need continued calcineurin inhibitor for many years. While MMF as monotherapy has not been shown to be effective (23), MMF in combination with steroids may induce remissions as effectively as alkylating agents; however, post-treatment relapse occurs in 75% of patients (24). Rituximab has been shown to induce remission in several studies to date (25–27), with decline in proteinuria occurring several months after dosing. Optimal dosing regimen, retreatment schedule, and long term effects, however, are yet to be corroborated by large trials. Finally, synthetic ACTH has been shown to be effective in reducing proteinuria (28–30) and similar results are evident with use of ACTH gel in the United States; however studies are small, and long term outcomes have not been determined (31).

Recent Kidney Disease Improving Global Outcomes guidelines recommend an initial immunosuppressive...
regimen of cyclophosphamide with corticosteroids (32). However, there is reluctance to use cyclophosphamide, mostly due to immediate and potential long term adverse effects. Risk for malignancy remains a long term concern, given increased cumulative doses of cyclophosphamide in the case of relapses. In this issue of CJASN, van den Brand et al. investigated the incidence of cancer in a cohort of IMN patients, treated with cyclophosphamide (33). All patients achieved age appropriate cancer screening at time of induction, in addition to measurement of anti–phospholipase A2 receptors antibodies. During a median follow-up time of 6 years, the incidence of cancer was 21.2 per 1000 patient-years in cyclophosphamide-treated patients compared with 4.6 per 1000 patient-years in those not receiving cyclophosphamide. There was an adjusted incidence ratio for cyclophosphamide exposure of 3.2 and, thus, a 3-fold increase in cancer risk.

Previous studies involving cyclophosphamide use in Wegener’s granulomatosis indicated an increased risk of malignancy with cumulative doses $>50$ g (17,34). A more recent study of cumulative cyclophosphamide doses $>36$ g, however, revealed significantly increased incidence ratio for acute myelogenous leukemia, bladder cancer, and non-melanoma skin cancer with increased risk of malignancy (35). Similarly, older literature for cyclophosphamide use in rheumatoid arthritis revealed a 4-fold increase in overall incidence of malignancies, with significant differences in mean dose of the study groups (36). The van den Brand study confirms much of the information about cyclophosphamide in the literature from other studies but with several differing findings, such as lack of a dose response for cyclophosphamide and malignancy, and a low incidence of bladder cancer. Indeed, one could ponder whether malignancy associated with cyclophosphamide might be influenced by the type of underlying autoimmune disease afflicting a patient.

There are some limitations of the van den Brand study, including its small size of 272 patients, with only 127 with cyclophosphamide exposure. Because it is a single center study with a homogeneous racial and genetic profile, it may be difficult to apply study findings to the general population. In addition, there may be genetic differences in response to cyclophosphamide with regard to both treatment response and malignancy risk. The cyclophosphamide group included older male patients more predisposed to malignancies at baseline. In addition to the confounders analyzed in the study, other occupational and environment exposures may be worth exploring, given the increased risk of bladder and hematologic malignancies generally observed with cyclophosphamide. Specific details involving postexposure cancer screening would also be helpful in determining special screening protocols for exposed groups in the future. Although the study found an increased malignancy risk in the control group compared with the general population, it likely is a result of differing implementation of cancer screening protocols in the general population. A particular strength of the current study is the relatively uniform protocol for immunosuppressive treatment, although alternative immunosuppressive drugs were occasionally prescribed. While no specific dose-response relationship was observed, only 20% of patients received $>50$ g of cyclophosphamide.

The overall malignancy risk of cyclophosphamide for IMN must be balanced against the risk of ESRD and its associated comorbidities and complications. Long term outcomes of newer agents are yet to be determined. Future direction of IMN treatment should involve larger multicenter head-to-head trials comparing novel agents with standard treatment regimens. Longer follow-up durations are needed to fully understand the spectrum of malignancies as well as other outcomes necessitating specific post-treatment screening regimens in exposed patients.

The clinician is thus faced with a variety of options for treatment of IMN and must advise the patient about the effectiveness of therapy, immediate and long term side effects, impact on quality of life (QOL), and cost. Table 1 is the price at our institution to purchase the medications generally used for IMN for a 70 kg individual. Dose and duration will obviously change the totals, but the table is meant to serve as a reference point. As Table 1 illustrates, the costs of different therapies vary widely.

**Table 1. Cost of various therapies for membranous nephropathy for a 70-kg individual**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
<th>Unit Cost</th>
<th>Cost for 70-kg Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>80 units of corticortin (Acthar)</td>
<td>80 U/ml, 5 ml vial</td>
<td>$328,910</td>
</tr>
<tr>
<td></td>
<td>2×/wk×6 mo (26 wk/yr)</td>
<td>1 vial, $31,626</td>
<td>$328,910</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>100–200 mg/d</td>
<td>50 mg, $3.15</td>
<td>$3449</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>0.2 mg/kg</td>
<td>2 mg, $8.82</td>
<td>$5557</td>
</tr>
<tr>
<td></td>
<td>3 mo×30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1.50 mg/kg×12 mo</td>
<td>50 mg, $3.88</td>
<td>$2974</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3.5 mg/kg×12 mo</td>
<td>100 mg, $5.55</td>
<td>$4963</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>3 g×3 doses/yr</td>
<td>1 g, $22.34</td>
<td>$210</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>2 g/d×12 mo, generic CellCept</td>
<td>500 mg, $0.57</td>
<td>$832</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg, $12.53</td>
<td>$18,294</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.5 mg/kg×12</td>
<td>20 mg, $0.20</td>
<td>$128</td>
</tr>
<tr>
<td>Rituximab</td>
<td>275 mg/m²×4</td>
<td>100 mg, $656</td>
<td>$17,023</td>
</tr>
<tr>
<td></td>
<td>1 g/d×2</td>
<td>1 mg, $1.51</td>
<td>$1929</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone.
van den Brand et al. also addressed the QOL issue, but the significant difference in QOL of thrice weekly dialysis and its side effects cannot be understated relative to nondialysis. Patients must be given the option of balancing the increased risk of therapy and nondialysis with the unfavorable QOL effects of dialysis. As noted by the authors, not only is QOL on dialysis an important factor, but overall survival on dialysis is quite poor, a fact not often considered in discussing cancer risk with cyclophosphamide. Indeed, the risk of dying for ESRD patients is greater than that from most forms of cancer. Finally, despite the largess of the United States medical system, the financial cost for dialysis is high, not to mention the impact on self-esteem, ability to work, and social and family interactions. Different global health systems may find the financial constraints of some IMN treatments and dialysis challenging.

The competencies that we teach our trainees include Medical Knowledge, Communication, and System-Based Practice. We have a responsibility for presenting all available options to our patients. Patients then have the responsibility to choose. The van den Brand report assists us in these responsibilities to our patients and society in approaching treatment of IMN. On balance, cyclophosphamide with prednisone may still be a persuasive option for patients, financial cost for dialysis is high, not to mention the impact on self-esteem, ability to work, and social and family interactions. Different global health systems may find the financial constraints of some IMN treatments and dialysis challenging.

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None.

References

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