Cytotoxic therapy for membranous nephropathy and renal insufficiency: improved renal survival but high relapse rate


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Abstract

Background. Patients with idiopathic membranous nephropathy (iMN) and renal insufficiency have a high risk for progression to end-stage renal disease (ESRD). In the short term, treatment with oral cyclophosphamide and steroids attenuates the deterioration of renal function in these patients; however, the long-term efficacy is unknown.

Methods. We have studied prospectively 65 patients with iMN and renal insufficiency (serum creatinine >135 μmol/l) who were treated with oral cyclophosphamide (1.5–2.0 mg/kg/day for 12 months) and steroids (methylprednisolone pulses 3 × 1 g, i.v. at months 1, 3 and 5, and oral prednisone 0.5 mg/kg/48 h for 6 months).

Results. Follow-up was 51 (5–132) months. Renal function temporarily improved or stabilized in all patients. A partial remission (PR) occurred in 56 patients followed by a complete remission (CR) in 17. During follow-up, 11 patients had relapsed (28% relapse rate after 5 years), of whom nine were re-treated because of renal function deterioration. At the end of follow-up, 16 patients were in CR, 31 in PR, eight had a persistent nephrotic syndrome, one had mild proteinuria, four had progressed to ESRD and five had died. Overall renal survival was 86% after 5 years and 74% after 7 years, compared with 32% after 5 and 7 years in a historical control group.

Treatment-related complications occurred in two-thirds of patients, mainly consisting of bone marrow depression and infections. One patient has developed bladder cancer, another patient prostate cancer.

Conclusions. Renal survival is good if patients with iMN and renal insufficiency are treated with oral cyclophosphamide. However, side effects occur frequently and relapse rate is high during longer follow-up.

Keywords: cyclophosphamide; immunosuppressive therapy; kidney failure; membranous nephropathy; nephrotic syndrome; prednisone; proteinuria

Introduction

Idiopathic membranous nephropathy remains the most common cause of the nephrotic syndrome in adults [1]. Studies on the natural history of the disease show that up to 40% of untreated patients will progress to end-stage renal disease (ESRD) [2–5].

The immunosuppressive treatment of idiopathic membranous nephropathy is still a matter of debate. Some authors advocate immunosuppressive treatment for all patients with idiopathic membranous nephropathy and nephrotic syndrome, based on a randomized controlled trial conducted in Italy, clearly demonstrating that treatment with a combination of chlorambucil and prednisone improves renal survival in patients with idiopathic membranous nephropathy [4]. However, other authors argue rather strongly against the need for immunosuppressive treatment in view of the observed benign course in >50% of patients [3]. Therefore, we and others are in favour of restricting immunosuppressive therapy to patients at highest risk of developing ESRD (reviewed in [6]) [5,7–11].

In patients with idiopathic membranous nephropathy, various risk factors for the development of renal failure have been identified (reviewed by Reichert et al. [12]). However, the sensitivity and specificity of most factors are too low to justify their use to guide decisions on the start of immunosuppressive therapy [12]. It is evident, however, that an established deterioration of renal function is a powerful predictor of ESRD [2,8,10,12]. Therefore, most would agree that a trial of immunosuppressive therapy is warranted in such patients with idiopathic membranous nephropathy and renal function deterioration. We previously have shown that immunosuppressive treatment can
Immunosuppression for membranous nephropathy

attenuate the deterioration of renal function in these patients [6,7]. In this group of patients, treatment with oral cyclophosphamide and steroids seemed more effective and less toxic than the combination of chlorambucil and steroids (overview of the literature data in [6]). Admittedly, there are no controlled trials that document the efficacy of immunosuppressive therapy in patients with idiopathic membranous nephropathy and established renal insufficiency. Furthermore, most data are derived from small studies with short follow-up (overview of the literature in [6]) [5,7,10]. A recent study demonstrated that the renal outcome was better in patients with idiopathic membranous nephropathy and renal failure who were treated with the combination of chlorambucil and prednisone when compared with historical controls [10].

Since June 1991, we have prospectively studied patients with idiopathic membranous nephropathy and renal insufficiency. The data of these patients, who have been treated with oral cyclophosphamide and steroids, form the basis of this report. Our study comprises the largest patient cohort described so far.

Subjects and methods

We included only adult patients (age >18 years) with a biopsy-proven membranous nephropathy in whom a secondary cause of membranous nephropathy was excluded on clinical and/or laboratory grounds. Patients were recruited in our University Hospital or in one of the 19 referring hospitals. Eligible patients had to have evidence of renal insufficiency (defined as a serum creatinine >135 μmol/l, a calculated endogenous creatinine clearance <70 ml/min or a rise in serum creatinine of >50%) and a proteinuria of at least 2.0 g/10 mmol creatinine. Exclusion criteria were systemic diseases, malignancies, active infection, pregnancy or inadequate contraception, unstable angina pectoris, diabetes mellitus type I or long-lasting diabetes mellitus type II, clinical evidence of renal vein thrombosis, liver test abnormalities (>2 × upper limit of normal), active peptic ulcer disease or gastrointestinal diseases that could impair the resorption of oral medication. Patients who used immunosuppressive therapy in the previous 6 months were not eligible, except in the case of evident failure of treatment.

Details of the immunosuppressive treatment have been described [7]. In brief, treatment consisted of 1.5–2.0 mg/kg/day of oral cyclophosphamide, for 1 year, 1 g of methylprednisolone i.v. for three consecutive days at the beginning of the first, third and fifth month, and 0.5 mg/kg of oral prednisone every other day for 6 months with subsequent tapering. For the prevention of gastric complaints, famotidine was added, and to prevent Pneumocystis carinii pneumonia, most patients received 480 mg of trimethoprim-sulfamethoxazole daily in the first 4–6 months. All patients were advised to follow a moderately salt-restricted diet. Conservative treatment was not standardized; however, physicians were instructed to lower blood pressure aggressively. More recently, it has become practice to use angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers for all patients with proteinuria, and to add cholesterol-lowering therapy. Anticoagulant drugs were not prescribed routinely.

For survival analysis, the time of follow-up started at the beginning of treatment with cyclophosphamide and steroids. Follow-up continued until September 2002, or ended at the time of death or the onset of ESRD.

Patients were seen regularly during follow-up, every 4–8 weeks during treatment and every 3–4 months thereafter, but less frequently in cases where complete remission (CR) occurred. Blood pressure, complications of the nephrotic syndrome, side effects of the therapy and laboratory data were registered. To correct for inappropriate 24 h urine collections, the amount of proteinuria was expressed as a protein-creatinine index (g/10 mmol creatinine). A CR of proteinuria, partial remission (PR), persistent proteinuria and nephrotic range proteinuria were defined as a protein-creatinine index of ≤0.2, 0.21–2.0, 2.1–3.4 and ≥3.5 g/10 mmol creatinine, respectively, where in the case of remission, renal function should have improved or at least stabilized. All patients who entered a CR were also registered as having a PR. Relapses were defined as nephrotic range proteinuria after a PR or CR of the proteinuria or a rise in proteinuria of >50% in patients in whom proteinuria had improved initially with >50%, without reaching values ≤2.0 g/10 mmol creatinine.

A second course of immunosuppressive therapy was offered to patients who relapsed to nephrotic range proteinuria together with a rise in serum creatinine of >50% over the lowest value attained during or after the first course of cyclophosphamide treatment.

The historical controls (n = 24) consisted of patients with an idiopathic membranous nephropathy and renal insufficiency (serum creatinine >135 μmol/l) referred to our University Hospital for therapeutic advice or inclusion in therapeutic trials, and thus came to our attention in the same way as the patients included in this cohort study. Several of these historical control patients were included in former trials and treated with prednisone monotherapy (n = 7), i.e. cyclophosphamide (n = 1) or both (n = 3). Since these treatment modalities have proved ineffective [9,13], these patients can be considered historical controls. Most of the historical control patients were not treated with immunosuppressive therapy at all (n = 13), mainly because we were not used to doing so before June 1991.

Calculations and statistics

For descriptive statistics, results are given as means ± SD, or medians with range when appropriate. Mean arterial blood pressure (MAP) was calculated using the formula MAP = diastolic blood pressure + 1/3 × (systolic blood pressure – diastolic blood pressure). For calculations of renal survival, the time of renal death was defined as the start of renal replacement therapy or the time of death. The cumulative probabilities of a clinical event (death, ESRD, PR, CR or relapse of nephrotic syndrome) were estimated according to Kaplan and Meier. The log rank test was used to compare survival curves. To demonstrate further an effect of the immunosuppressive therapy on the rate of deterioration of renal function, we have calculated the slope of 1000/serum creatinine vs time before and after the start of the treatment for the treated patients and overall for the historical controls. The Mann–Whitney test was used for
comparison between groups, and Wilcoxon signed rank test for comparisons within the group of treated patients. A $P$-value of $<0.01$ was considered significant. All statistical procedures were done using SPSS software (SPSS version 10.0, Chicago, IL).

### Results

Baseline characteristics of the treated patients are given in Table 1.

Most patients ($n=59$) started immunosuppressive therapy because of a serum creatinine $>135\mu$mol/l, and six patients started immunosuppressive therapy because of a 50% increase in serum creatinine. Calculated endogenous creatinine clearance (Cockcroft formula) in the latter group was 86 (51–109) ml/min/1.73 m$^2$, proteinuria 10.2 (4.5–16.0) g/10 mmol creatinine and serum albumin 23 (17–30) g/l. Inclusion of these patients did not influence the results.

Nineteen patients (29%) had received previous immunosuppressive therapy, mainly consisting of short-term high-dose prednisone ($n=7$), prednisone followed by a combination of prednisone and chlorambucil ($n=3$) or only a combination of prednisone and chlorambucil ($n=6$). Four patients had received immunosuppressive therapy <6 months before the start of cyclophosphamide treatment, but this previous treatment had failed as evidenced by progressive renal insufficiency. Follow-up after the start of therapy averaged 51 months (SD 30 months, range 5–132 months). Twenty-one patients have been followed for >5 years.

Median values of MAP, serum creatinine, serum albumin, serum cholesterol, proteinuria and creatinine clearance, before, at regular intervals after the start of therapy and at the end of follow-up, are given in Table 2. At the start of cyclophosphamide treatment, blood pressure was reasonably well controlled, and 78% of patients were treated with an ACE inhibitor and/or angiotensin receptor blocker. Blood pressure further improved during follow-up, although antihypertensive treatment was not intensified.

Serum creatinine improved by >10% in 91% of patients during the first year. In only three patients (4.6%) was serum creatinine increased by >10% Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>55:10</td>
</tr>
<tr>
<td>Age at clinical onset of disease (years)</td>
<td>50 (15–77)</td>
</tr>
<tr>
<td>Age at time of biopsy (years)</td>
<td>51 (15–77)</td>
</tr>
<tr>
<td>Interval between biopsy and start of cyclophosphamide (months)</td>
<td>13 (0–280)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>171 (106–512)</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>23 (9–43)</td>
</tr>
<tr>
<td>Proteinuria (g/10 mmol creatinine)</td>
<td>10.0 (2.0–23.0)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m$^2$)</td>
<td>42 (13–109)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>102 (80–133)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>51 (5–132)</td>
</tr>
</tbody>
</table>

Values are median with range.

Table 2. Laboratory parameters and blood pressure during treatment and follow-up

<table>
<thead>
<tr>
<th>Start therapy ($n=65$)</th>
<th>12 months ($n=60$)</th>
<th>24 months ($n=51$)</th>
<th>End follow-up ($n=65$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S creatinine (µmol/l)</td>
<td>129* (68–376)</td>
<td>129** (74–337)</td>
<td>128* (69–1000)</td>
</tr>
<tr>
<td>S albumin (g/l)</td>
<td>22 (13–42)</td>
<td>23 (9–43)</td>
<td>23 (7–54.4)</td>
</tr>
<tr>
<td>S cholesterol (µmol/l)</td>
<td>7.7 (5.0–28.8)</td>
<td>7.6 (4.2–23.2)</td>
<td>10.0 (2.0–23.0)</td>
</tr>
<tr>
<td>Proteinuria (g/10 mmol creatinine)</td>
<td>8.9* (3.4–17.9)</td>
<td>8.9* (0–4.3–14.0)</td>
<td>4.8* (0–34.2)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m$^2$)</td>
<td>61** (22–170)</td>
<td>60** (16–138)</td>
<td>60** (16–138)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>92 (69–118)</td>
<td>92 (69–118)</td>
<td>92 (69–118)</td>
</tr>
</tbody>
</table>

Values are median with range. The superscripted * indicates $P<0.01$, ** indicates $P<0.001$, compared with values at the start of treatment.
during the treatment year. The lowest serum creatinine value attained after the start of treatment was 107 (70–489) µmol/l and this nadir was reached after a median of 6 months. Immunosuppressive therapy attenuated the deterioration of renal function as indicated by the change in the median slope of 1000/serum creatinine from –3.01/µmol/year before to 0.12 l/mmol/year after the start of therapy (P < 0.001).

Proteinuria also decreased in the majority of patients. This decrease in proteinuria was gradual, and continued even after the end of the immunosuppressive treatment (Table 2). As can be expected, serum albumin improved and cholesterol declined after the start of treatment (Table 2).

Overall, 56 patients have developed a PR of proteinuria after an average of 10.6 months. In 17 patients, proteinuria further decreased to values ≤0.2 g, and this CR was reached 12 (0–38) months after the onset of the PR. The cumulative incidence of PR is 92% after 5 years and of CR is 36% after 5 years (Figure 1). Not all patients have remained in stable remission. Of the 17 patients who developed a CR, one relapsed to nephrotic range proteinuria. Of the 39 patients who have developed only a PR of proteinuria, 10 relapsed to nephrotic range proteinuria. Relapsing patients had been in remission for 27 (7–66) months. The cumulative incidence of relapses is 28% at 5 years after onset of the remission (Figure 2). In most relapsing patients, serum creatinine eventually has increased by >50%. The occurrence of a relapse could not be predicted by the serum creatinine, the amount of proteinuria or MAP at the start of therapy.

The overall course in our patient group and the status at the end of follow-up are depicted in Figure 3. Thus far, nine patients have been re-treated because of a relapse and again deteriorating renal function. At the end of the follow-up, 16 patients were in CR, 31 patients in PR, eight patients have a persistent nephrotic syndrome and one patient has mild persistent proteinuria. Four patients have reached ESRD; in three of these, serum creatinine was ≥400 µmol/l at the start of treatment. Five patients have died at a median of 2.7 years after the start of therapy.

Of the group of patients that started immunosuppressive therapy because of a 50% rise in serum creatinine (n = 6), two patients were in CR (33%), three in PR (50%) and one had a persistent nephrotic syndrome (17%).

Outcome was similar in patients who had received immunosuppressive therapy prior to starting cyclophosphamide (n = 19) and patients who had not been treated before. Also, when analysing the data separately for patients with a serum creatinine below or above the median value of 171 µmol/l at the start of therapy, no differences in outcome were noted. A PR or CR of proteinuria developed in 43 out of 51 patients using an ACE inhibitor or angiotensin receptor antagonist as compared with 13 out of 14 patients who did not use these agents (P = NS). The use of an ACE inhibitor or angiotensin receptor antagonist also did not influence renal survival rate or death (7/51 vs 2/14; P = NS). We also did not observe an effect of blood pressure values on remission rate or renal outcome.

In our study, renal survival without censoring for death is 86% at 5 years and 74% at 7 years after the start of treatment. We have compared renal survival in our treated patients with renal survival in a group of 24 historical controls. In these historical controls, renal survival was 32% at 5 years, a highly significant difference (P < 0.001; Figure 4). Results are similar if only untreated control patients are included in the analysis.

The beneficial effect of cyclophosphamide therapy in attenuating deterioration of renal function is also obvious if we compare the slopes of 1000/serum creatinine: 0.121/µmol/year with cyclophosphamide compared with –1.211/µmol/year in the historical controls (P < 0.001).

Five patients have died, at a median age of 63 (43–79) years. Two patients died suddenly, at home of unknown causes while in CR or PR. One patient died from cardiovascular disease while being re-treated. One patient died due to sepsis, in CR 7 months after the completion of immunosuppressive treatment. The fifth patient died of a disseminated bladder carcinoma, which he developed 21 months after the start of therapy. This patient had received a cumulative dose of 20 g of cyclophosphamide. Patient survival is 91% after 5 years and 84% after 7 years.
Side effects were frequent. Of 65 patients, 43 experienced one or more side effects during the treatment year. Bone marrow depression and infectious complications were most frequent (Table 3). In most patients, the dose of cyclophosphamide was temporarily reduced (Table 3). Only four patients (6%) had to stop cyclophosphamide within 6 months after the start of treatment; in two patients, azathioprine was used as replacement.

Thromboembolic complications occurred in three patients after the start of treatment. Two patients have developed a malignancy after treatment: one patient developed a bladder carcinoma (see above) and one patient a prostate carcinoma.

Discussion

Our study clearly demonstrates that treatment with oral cyclophosphamide and prednisone improves renal survival in patients with idiopathic membranous nephropathy and renal insufficiency. Admittedly, we have not performed a randomized, controlled trial. However, our study represents the largest cohort of treated patients studied prospectively over a long time period. If we compare renal survival in our treated patients with that in a group of historical controls from our centre, there is a clear survival difference (5 year renal survival 86% vs 32%). We have also compared our results with data reported by other investigators. In untreated patients with idiopathic membranous nephropathy and renal insufficiency, reported renal survival rates range from 20 to 30% after 7 years [8,10]. Moreover, our renal survival rate is even higher than those reported for untreated patients with idiopathic membranous nephropathy and normal renal function [2,4]. Our study thus supports the conclusions from recent smaller studies that immunosuppressive therapy improves outcome in patients with idiopathic membranous nephropathy and normal renal function [8,10]. Apparently, these conclusions do not hold for all immunosuppressive regimens containing cytotoxic drugs. Falk et al. have reported that i.v. cyclophosphamide did not offer additional benefits [9]. In a randomized study, we also demonstrated that i.v. cyclophosphamide was not effective [13]. Azathioprine with oral prednisone, without methylprednisolone infusions, has also been used without success, as reported in a retrospective study [14]. In contrast, chlorambucil has been used with apparent success [5,6,10]. However, in our experience, chlorambucil may be less effective than cyclophosphamide and causes more side effects [6].

Based on the findings of the randomized trials conducted by Ponticelli et al. [4] and our present and previous observations, we feel that it is no longer justified to withhold treatment from patients with idiopathic membranous nephropathy and renal failure. Therefore, it might be impossible to perform a placebo-controlled trial. Although the results of our study seem favourable, we cannot definitively answer the question of whether the start of immunosuppressive therapy can be delayed until renal insufficiency develops. In the study of Ponticelli et al., 10 year renal survival was 92%, a value which is better than our 74% renal

Fig. 3. Flow chart of treatment results. CR = complete remission = proteinuria ≤0.2 g/10 mmol creatinine; PR = partial remission = proteinuria 0.2–2.0 g/10 mmol creatinine; PP = persisting proteinuria = proteinuria 2.1–3.4 g/10 mmol creatinine; (R)NS = (recurrent) nephrotic syndrome = proteinuria ≥3.5 g/10 mmol creatinine; ESRD = end-stage renal disease. Status at the end of follow-up is given in the grey rectangles.

Fig. 4. Renal survival. Renal survival for treated patients (n = 65) was 86% after 5 years and 74% after 7 years; for historic controls (n = 24), it was 32% after 5 years, the difference being significant (P < 0.0001).

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survival after 7 years. However, patients were not comparable at all since we included only high risk patients whereas in the Italian randomized study patients were included with a lower predicted risk, as indicated by the short duration of disease and the almost normal renal function at the start of therapy. Furthermore, we have calculated renal survival from the time of starting immunosuppressive therapy, which evidently causes an underestimation of survival rate. If we calculate renal survival from the time of renal biopsy, estimated 5, 7 and 10 year renal survival rates are 93, 90 and 81%, respectively.

Thus far, five patients have died. None of the patients died of renal failure. In one patient, who died from bladder carcinoma, death may have been related to treatment. The other patients died long after the end of treatment, most frequently from cardiovascular causes. Patient survival of 91% at 5 years and 84% at 7 years is comparable at all since we included only high risk patients whereas in the Italian randomized study patients were included with a lower predicted risk, as indicated by the short duration of disease and the almost normal renal function at the start of therapy.

Our study also illustrates some major drawbacks of our immunosuppressive protocol, i.e. a relatively high rate of relapses, frequent side effects, and lack of effectiveness in some patients.

Overall, a quarter of the patients entered a CR during follow-up. It is of note that in most patients, the time of onset of CR was >12 months after the start of immunosuppressive therapy. Prognosis is excellent in patients who have developed a CR, since thus far only one of these patients (6%) has relapsed. In contrast, relapses have occurred frequently in patients who responded to treatment with a PR (10 out of 39 patients, 26%) or a >50% reduction in proteinuria, and may even increase with longer follow-up. Cumulative incidence of relapses after the occurrence of a PR or CR is 28% after 5 years. We find this relapse rate rather high; however, similar figures (30% after 2 years) have been reported by Ponticelli et al. for patients with membranous nephropathy and preserved renal function treated with either cyclophosphamide or chlorambucil [15]. In most of our patients who relapsed, renal function has deteriorated, necessitating a new course of immunosuppression.

Many patients experienced complications from the immunosuppressive therapy, especially bone marrow depression and infectious complications. This high incidence of side effects may be partly related to the decreased renal function of our patients [5–7]. In only 6% of patients did the severity of side effects necessitate a premature termination of therapy (<6 months). One feared side effect of cyclophosphamide therapy is the development of neoplasias, in particular bladder cancer [16, 17]. It has been shown that the risk of cyclophosphamide-related bladder cancer increases with the duration (especially >2.7 years) and the cumulative dosage (mainly >100 g) of cyclophosphamide treatment. Bladder carcinoma can become manifest even after a latency period of more than a decade [16, 18].

The side effects of alkylating agents increases the urgency of the search for less toxic therapies. Recently, reports have become available regarding the treatment of patients with therapy-resistant or relapsing idiopathic membranous nephropathy with mycophenolate mofetil. Short-term results show substantial reductions of proteinuria, although remissions were scarce, mostly accompanied by preservation of renal function. Furthermore, mycophenolate mofetil was well tolerated [19, 20]. Further results are awaited.

We feel that our data are sufficient to support the proposal of a formal comparison between early and late start of immunosuppressive therapy. Admittedly, an earlier start of immunosuppressive therapy poses a risk to some patients who would have developed a spontaneous remission of proteinuria. However, an earlier start of treatment might result in even better renal survival rates, may be associated with fewer and less severe side effects, and might result in a lower rate of relapses. Patients to be included in such studies could be selected based on defined risk factors for progressive disease such as the duration and magnitude of proteinuria or the urinary excretion of IgG, β₂-microglobulin or α₁-microglobulin [12].

In conclusion, treatment of patients with idiopathic membranous nephropathy and renal insufficiency with oral cyclophosphamide and steroids results in a high
remission rate and good renal survival, suggesting that immunosuppressive treatment is still effective when started at a time point when renal insufficiency has developed. We cannot answer the question of whether an earlier start of treatment would have been more beneficial. A formal study is warranted. Our treatment schedule with cyclophosphamide and steroids is hampered by the frequent occurrence of side effects. Unfortunately, relapses are also frequent with longer follow-up. Therefore, we need to continue studies in search of safer and more effective therapeutic agents.

Acknowledgements. P.B.-V. is supported by a grant from the Dutch Kidney Foundation (NSN; PC132) and A.B. by a grant from the Dutch Science Foundation (NWO-MW 920-03-038). The following colleagues have actively participated in this study of the Membranous Nephropathy Study Group: Dr A. J. Apperloo, St Elisabeth Hospital, Tilburg; Professor Dr J. H. M. Berden and Dr H. W. van Hamersvelt, University Medical Center St Radboud, Nijmegen; Drs J. J. Beutler, A. Hollander, J. L. J. Jansen and M. I. Koolen, Jeroen Bosch Hospital, ’s Hertogenbosch; Dr P. A. Bleeker, Hospital Rivierenland, Tiel; Drs F. H. Bosch and K. J. Parlevliet, Rijnstate Hospital, Arnhem; Dr M. A. G. J. ten Dam, Canisius Wilhelmina Hospital, Nijmegen; Dr P. Douwes-Draaijer, Catharina Hospital, Eindhoven; Drs G. W. Feith and M. den Hartog, Hospital Gelderse Vallei, Ede; Dr L. A. M. Frenken, Atrium Medical Center, Heerlen; Drs W. Grave and J. J. J. M. Wirtz, Laurentius Hospital, Roermond; Dr J. G. M. Jordans, Medical Spectrum Twente, Enschede; Dr A. G. Lieverse, Maxima Medical Center, Eindhoven; Drs A. J. Luik and C. M. C. Verstappen, Hospitals Noord-Limburg, Venlo; Drs T. C. Noordzij and H. P. C. van Roermund, Francisius Hospital, Roosendaal; Dr R. E. H. Smeets, St Anna Hospital, Geldrop; Dr P. F. M. J. Spooren, TweeSteden Hospital, Tilburg; Dr R. L. Stuyver, Hospital Velp, Velp; Dr G. P. Verburg, Amphia Hospital, Breda; Dr C. G. Vermeij, Deventer Hospital, Deventer; and Dr A. W. L. van den Wall Bake, Maxima Medical Centrum, Veldhoven.

Conflict of interest statement. None declared.

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Received for publication: 25.8.03
Accepted in revised form: 20.11.03