Membranous nephropathy – Role of alkylating agents

Date written: July 2005
Final submission: September 2005
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GUIDELINES

a. **Treatment with alkylating agents is associated with an increased rate of remission in patients with nephrotic syndrome and idiopathic membranous nephropathy when compared to steroid therapy alone or no therapy. (Level I evidence)**

b. **There is insufficient data to confirm that this effect translates into an improvement in renal outcomes. (Level I evidence)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV evidence)

Who to treat?

- **To avoid possibly unnecessary treatments and toxicity, most clinical studies have focused on individuals who are thought to be at risk for progressive disease. Consequently, at this time, the clinical use of alkylating agents in membranous nephropathy should be restricted to individuals with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function and/or reduced response to supportive therapy.**

- **A variety of models incorporating a range of clinical and histological features have been validated, with the ability to predict the development of chronic renal insufficiency of up to 86%, with a sensitivity of more than 60% (Cattran 1998, Cattran et al 1997). Such a model could be used to target therapy by identifying individual patients at risk for progressive disease. Treatment algorithms based on these models have been proposed (Cattran 1998). These have not been tested in large-scale trials.**

- **Currently, there is no evidence to support disease-specific intervention in adult patients with good prognostic features (proteinuria < 3 g/day and normal renal function), although supportive therapy including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system would seem prudent. (Level IV evidence) Nonetheless, long-term follow-up is still required to monitor for the development of adverse indicators to identify additional patients at risk for progressive kidney disease. (Level IV evidence)**

When to treat

- **The possibility of spontaneous remission has led many authors to suggest that a 6-month period on conservative therapy (including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system) may be valuable before embarking on cytotoxic therapy. (Level IV evidence)**

- **While most studies have dealt with early treatment of patients with adverse prognostic features (and excluded patients with established renal impairment) there have been a few small studies to suggest that even late intervention may be efficacious (Bruns et al 1991, Mathieson et al 1988). (Level III evidence)**

- **Although such studies imply that a brief delay may not be harmful, the progression of control patients over a short period in many of the trials described below should mean this course should only be conducted with cautious observation. (level IV evidence)**

Background

Idiopathic membranous glomerulonephritis (MGN) runs a variable course. Most patients do well, with 10-year renal survival of 70-90% (Schieppati et al 1993). Spontaneous remissions occur in up to 65% of patients (Geddes et al 2000), sometimes months or years after the onset of nephrotic syndrome and a substantial percentage of patients never progress to renal failure. To avoid possibly unnecessary treatments, most clinical studies have focused on individuals who are thought to be at greater risk for progressive disease. The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of alkylating agents on renal functional decline in MGN with poor prognostic features, such as heavy proteinuria (>3 g/24 h), impaired renal function at presentation, deteriorating renal function and/or reduced response to therapy.

Search strategy

Databases searched: MeSH terms and text words for Membranous Nephropathy were combined with MeSH terms and text words for alkylating agents. This search was carried out in Medline (1966 to September Week 1 2004). The Cochrane Renal Group Trials Register was also searched for trials of membranous nephropathy not indexed in Medline.

Date of searches: 9 September 2004.

What is the evidence?

There have been a number of small, prospective, randomised controlled trials (RCTs) comparing alkylating agents with no treatment.

There have been four RCTs of alkylating agents alone or in combination with steroids, which have compared treatment responses with those observed in patients receiving therapy compared to no therapy or placebo.

- In the earliest RCT, Donadio et al (1974) conducted a prospective study of 22 patients randomised to either oral cyclophosphamide of 1.5–2.5 mg/kg daily for a period of 12 months or no specific therapy. They were unable to demonstrate in this small study any significant difference in renal function, proteinuria, or histological stage of disease in patients who received cyclophosphamide.

- Braun et al (1995) randomised 55 patients with idiopathic MGN to receive therapy with a cyclophosphamide or supportive care. After 60 months of follow-up, treatment modality had no effect on rates of remission or doubling of serum creatinine.

- Ponticelli et al (1992) initially studied the effect of 6 months of treatment with chlorambucil plus corticosteroids in monthly cycles vs. symptomatic therapy, in 62 patients with MGN. All patients had nephrotic range proteinuria. Patients with renal insufficiency were excluded Twenty three of 32 chlorambucil patients experienced a complete or partial remission compared with just 9 of 30 control patients. Ten years after initial therapy, the probability of renal survival was 0.92 for treated patients compared with 0.60 for controls. Some have criticized this study because of this apparently rapid rate of progression in this control group. ·

- Murphy et al (1992) studied 40 patients with idiopathic MGN randomised to receive either no treatment or a regimen of oral cyclophosphamide for 6 months, and warfarin and dipyridamole for 2 years. During the 2 years of the trial, renal function remained unchanged in both groups, but reduced proteinuria and improved serum albumin were found in the cyclophosphamide-treated patients. When only nephrotic patients are considered, a significantly higher proportion of patients in the treatment group achieved a complete remission compared with control patients (9 of 13 vs. 4 of 13, P = 0.05). As progressive deterioration in renal function in MGN is associated with persistent heavy proteinuria, they concluded that treatment with cyclophosphamide had a beneficial effect.

Four studies have evaluated the effect of adding an alkylating agent to a steroid-based regimen in the control arm.

- Ahmed et al (1994) examined the effect of prednisolone plus chlorambucil compared with prednisolone alone in 20 patients with idiopathic membranous nephropathy.

- Falk et al (1992) conducted a RCT of pulse methylprednisolone, oral corticosteroids, and 6 months of intravenous cyclophosphamide compared with oral alternate-day corticosteroids alone in 26 patients with idiopathic membranous nephropathy and clinical and laboratory evidence of deteriorating renal function. There were no differences in the numbers progressing to end-stage kidney disease (ESKD) or in the creatinine levels or urinary protein excretion over a mean follow-up period of 29 months.

- Pahari et al (1993) randomised 71 patients with idiopathic MGN to receive steroid and cyclophosphamide every other month and steroid alone. In patients receiving cyclophosphamine, 33 of 36 patients achieved complete remissions, 2 had a relapsing course with remission on further courses of therapy and only one has reached end-stage kidney failure (ESKF). In contrast, 15 of the 35 patients receiving steroids alone achieved complete remission and 7 a partial remission.

- In a second study by Ponticelli's (1995) group, 92 nephrotic patients were randomised to receive the same chlorambucil/steroid regimen or steroids alone. This confirmed a net benefit effect, with 90% survival in the chlorambucil-treated group at 10 years compared to 62% in the untreated group. However, treatment with chlorambucil and methylprednisolone was less likely to induce a remission in the presence of renal insufficiency or mesangial sclerosis.

Three meta-analyses of clinical trials in idiopathic membranous nephropathy have been published.

- Imperiale, Goldfarb, and Berns' (1995) analysis included the first five trials discussed above and some retrospective data. This analysis was confounded by a number of factors including heterogeneity in the doses and duration of drug therapy, mean duration of follow-up, definitions of complete and partial responses to treatment and comparison therapies used. Nonetheless, they concluded that treatment with cytotoxic agents benefited patients with idiopathic membranous nephropathy by inducing significantly more remissions than untreated groups.

- Hogan et al (1995) conducted a larger examination of 32 studies published between 1968 and 1993. The analysis incorporated data on close to 2000 patients followed, in most cases, for more than 2 years. The meta-analysis again found that the relative chance of complete remission was improved for patients treated with alkylating agents. At 5 years, the probability of renal survival in the steroid/no-therapy group (0.80) was lower than in patients receiving alkylating agents (0.99). However, the percentage of patients in the analysis included from RCTs was small, increasing the possibility of type II error.

- In the most recent meta-analysis (Schieppati et al, 2004), no beneficial effect on ESKD was observed in patients treated with alkylating agents (RR 0.56, 95%CI: 0.18–1.68, P = 0.3) when compared with placebo or no treatment. Nonetheless, alkylating agents induced more remissions than steroids (complete remission, RR 1.89, 95%CI: 1.34–2.67, P = 0.0003; complete or partial remission, RR 1.45, 95%CI: 1.16–1.81, P = 0.001). Overall, alkylating agents showed a significant effect on complete remission (RR 2.37, 95%CI: 1.32–4.25, P = 0.004) and final proteinuria (weighted mean difference, -2.36 g/24h; 95%CI: -4.27 to -0.46; P=0.02)

Three studies have compared the effect of two specific immunosuppressive treatments within the class of alkylating agents.

- Branten et al (1998) randomised patients with idiopathic membranous nephropathy and renal insufficiency to monthly cycles of steroids (1 g methylprednisolone IV on 3 consecutive days, followed by oral prednisone 0.5 mg/kg/day in months 1, 3 and 5) and chlorambucil (0.15 mg/kg/day in months 2, 4 and 6) (n=15); or oral cyclophosphamide (1.5-2.0 mg/kg/day for 1 year) and steroids in a comparable dose (n = 17). Twelve months after starting treatment, mean serum creatinine was lower in cyclophosphamide-treated patients than in those receiving chlorambucil ($P < 0.01$). In addition, four chlorambucil-treated patients developed ESKD, and five needed a second course of therapy, whereas only one cyclophosphamide-treated patient developed ESKD ($P < 0.05$). Remissions of proteinuria occurred more frequently after cyclophosphamide treatment (15/17 vs. 5/15; $P < 0.01$)

- Ponticelli et al (1998) compared regimens of methylprednisolone (1 g intravenously for 3 consecutive days followed by oral methylprednisolone, 0.4 mg/kg per d for 27 d) alternated every other month either with chlorambucil (0.2 mg/kg per d for 30 d) with oral cyclophosphamide (2.5 mg/kg per d for 30 d). All patients (n=87) had biopsy-proven membranous nephropathy and nephrotic syndrome. Eighty two per cent (36/44) assigned to steroid and chlorambucil developed complete or partial remission of their nephrotic syndrome, compared to 93% assigned to methylprednisolone and cyclophosphamide ($P = 0.1$). Relapse subsequently occurred in 25-30% of patients, with no differences between treatment groups. On average, renal function remained stable over the 3-year follow-up in both treatment groups.

- Reichert et al (1994) compared oral chlorambucil and intravenous cyclophosphamide-based drug regimens in the treatment of 18 patients with membranous nephropathy and deteriorating renal function. Therapy consisted of chlorambucil (0.15 mg/kg body weight per day orally in months 2, 4, and 6) and prednisone (three intravenous pulses of 1 g of methylprednisolone followed by oral prednisone at 0.5 mg/kg per day in months 1, 3, and 5) or intravenous cyclophosphamide (750 mg/m^2 body surface area once every month for 6 months) and methylprednisolone (three intravenous 1-g pulses in months 1, 3, and 5). Renal function was better preserved in patients receiving chlorambucil with a net reduction in serum creatinine levels in the group treated with chlorambucil and an increase in the group treated with intravenous cyclophosphamide (difference between groups, $P < 0.001$). At the end of follow-up, one patient in the chlorambucil group and four patients in the cyclophosphamide group required renal replacement therapy.

A meta-analysis of these studies (Schieppati et al 2004) concluded that there was no significant difference in the need for dialysis or transplantation or in the rates of complete, partial or for complete or partial remission between different alkylating agents.

Both cyclophosphamide and chlorambucil are associated with significant short- and long-term toxicity. In particular, the risk of bladder cancer is significantly increased by cyclophosphamide, many years after initiation of treatment and often well outside standard trial analysis. In one study in Wegener's granulomatosis, the bladder cancer risk was estimated to be 5% at 10 years and 16% at 16 years after first exposure to cyclophosphamide (Talar-Williams et al 1996). It is possible that a similar cancer incidence in membranous nephropathy may outweigh any benefit in slowing disease

progression. Some have suggested that intravenous route for cyclophosphamide may reduce bladder toxicity, however the only RCT to use pulsed cyclophosphamide plus prednisone showed no benefit compared with the use of steroids alone (Muirhead et al 1999). These risks associated with cyclophosphamide have led some to consider chlorambucil as the alkylating agent of choice for the treatment of MGN (Talar-Williams et al 1996). However, chlorambucil has a very narrow therapeutic index for marrow suppression. In the recent meta-analysis, cyclophosphamide treatment resulted in an overall lower rate of discontinuation due to adverse events compared to chlorambucil (RR 2.34, 95%CI: 1.25 –4.39, P = 0.008). In particular, leukopenia was less common in cyclophosphamide-treated patients compared to chlorambucil-treated patients.

Summary of the evidence

While there is evidence that cyclophosphamide or chlorambucil can induce remission of proteinuria in some cases of membranous nephropathy and nephrotic syndrome, the data is confounded by the inclusion in trials of patients who may have had spontaneous remission as well as by differences in study methodology. There is also currently insufficient evidence to demonstrate any benefit in terms of progressive renal impairment and ESKD. The optimal agent to use remains to be established.

Nonetheless, in patients with poor prognostic features, such as heavy proteinuria (> 3 g/24 h), impaired renal function at presentation, deteriorating renal function in whom after a period of monitoring, an inexorable decline in renal function appears likely, the possibility of inducing remission of proteinuria by using cytotoxic therapy should be balanced against the significant risk of toxicity.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: The alkylating agents cyclophosphamide and chlorambucil are both effective in the management of membranous nephropathy. Because of growing concern about long term toxicity, especially with cyclophosphamide, these drugs should be reserved for patients who exhibit clinical features, such as severe or prolonged nephrosis, renal insufficiency, or hypertension, that predict a high likelihood of progression to end-stage renal disease.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Ahmed et al, 1994	20	Randomised controlled clinical trial	Hospital, Bangladesh	20 patients with nephrotic syndrome and histological diagnosis of idiopathic membranous nephropathy	IV methylprednisolone 1 gm for 3 days, then oral prednisolone and chlorambucil	Prednisolone	15 mo	
Branten et al, 1998	32	Randomised controlled clinical trial	Hospital, Netherlands	32 patients with biopsy-proven membranous nephropathy	Chlorambucil and corticosteroids	Oral cyclophosphamide	38 mo	Partial randomisation
Donadio et al, 1974	22	Randomised controlled clinical trial	Renal clinic, US	22 adults with clinically- and Histologically-defined idiopathic membranous nephropathy	Oral cyclosporine	No intervention	12 mo	
Falk et al, 1992	26	Randomised controlled clinical trial	Multiple nephrology clinics, US	26 patients with biopsy-proven progressive membranous glomerulonephropathy	6 mo IV cyclophosphamide and pulse methylprednisolone corticosteroids	Alternate day corticosteroid alone	29 mo	

Table 1 Continued

Murphy et al, 1992	40	Randomised controlled clinical trial	University hospital, Australia	40 patients with idiopathic membranous glomerulonephritis	Oral cyclophosphamide at a maximum dose of 1.5 mg/kg/day; dipyridamole, sodium warfarin	No treatment	24 mo	
Pahari et al, 1993	36	Randomised controlled clinical trial	Hospital, India	36 patients with idiopathic membranous nephropathy	Steroid and cyclophosphamide	Steroid only	46 mo	
Ponticelli et al, 1998	95	Randomised controlled clinical trial	Multicentre, Italy	95 patients with biopsy-proven membranous nephropathy	Methylprednisolone and chlorambucil	Methylprednisolone and cyclophosphamide	At least 12 mo	
Ponticelli et al, 1995	81	Randomised controlled clinical trial	Multicentre, Italy	81 patients with idiopathic membranous nephropathy	Methylprednisolone and chlorambucil	Symptomatic therapy	60 mo	
Ponticelli et al, 1992	92	Randomised controlled clinical trial	Multicentre, Italy	92 patients with nephrotic syndrome caused by idiopathic membranous nephropathy	Alternating 1 month methylprednisolone and then chlorambucil for 6 months	Methylprednisolone for 6 months	54 mo	
Reichert et al, 1994	20	Randomised controlled clinical trial	University hospital and teaching hospitals in Netherlands	20 patients with nephrotic syndrome and biopsy-proven membranous nephropathy	Chlorambucil methylprednisolone and corticosteroids	Cyclophosphamide and methylprednisolone	6 mo – 36 mo	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Ahmed et al, 1994	Not specified	Not stated	Not stated	Not stated	Unclear	0.0%
Branten et al, 1998	Not specified	Not stated	Not stated	Not stated	Yes	0.0%
Donadio et al, 1974	Random number table	No	No	No	No	13.6%
Falk et al, 1992	Computer generated	No	No	No	Unclear	7.7 %
Murphy et al, 1992	Sealed envelopes	No	No	No	No	2.5 %
Pahari et al, 1993	Not specified	No	No	Not stated	No	14.1%
Ponticelli et al, 1998	Centre stratified random order	No	No	Not stated	No	8.4%
Ponticelli et al, 1995	Central	No	No	Not stated	Yes	23.5%
Ponticelli et al, 1992	Central	No	No	Yes	Yes	1.1%
Reichert et al, 1994	Not specified	Not stated	Not stated	Not stated	No	0.0%

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Ahmed et al, 1994	Urinary total protein excretion (g/day) after treatment	1.8 (3.14)	2.6 (2.2)	0.80 (95%CI:-3.18, 1.58)
	Serum Cr after treatment (g/d)	1.45 (0.35)	2.38 (2.28)	-0.93 (95%CI:-2.36, 0.50)
Branten et al, 1998	Serum creatinine (µmol/l) at 12 mo	216 (99)	174 (78)	42.00 (95%CI:-20.33, 0.50)
	Serum albumin (g/l) at 12 mo	32 (6.8)	40 (4.7)	-8.00 (95%CI: -12.10, -3.90)
	Proteinuria (g/10 mmol creatinine) at 12 mo	6.8 (4.4)	2.0 (3.0)	4.80 (95%CI:2.16, 7.44)
Donadio et al, 1974	Decrease in protein excretion (g/24 hr)	4.7 (3.2)	2.6 (3.5)	2.10 (95%CI: -0.91, 5.11)
Ponticelli et al, 1998	Mean proteinuria (g/d) at follow up	2.11 (2.87)	1.69 (2.36)	0.42 (95%CI:-0.68, 1.52)
	Mean plasma Cr (mg/dl) at follow up	1.25 (1.37)	1.32 (1.72)	-0.07, (95%CI: -0.72, 0.58)
Reichert et al, 1994	Creatinine (µmol/l)	260 (112)	218 (85)	42.00 (95%CI:-49.86, 133.86)

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Ahmed et al. 1994	Complete remission	5/10	3/10	1.67 (95%CI: 0.54, 5.17)	0.20 (95%CI:-0.22, 0.62)
	Partial remission	3/10	3/10	1.00 (95%CI:0.26, 3.81)	0.00 (95%CI:-0.40, 0.40)
	No response	2/10	4/10	0.50 (95%CI:0.12, 2.14)	-0.20 (95%CI:-0.59, 0.19)
	Developed renal insufficiency	1/10	2/10	0.50 (95%CI:0.05, 4.67)	-0.10 (95%CI:-0.41, 0.21)
Branten et al. 1998	ESRD	4/15	1/17	4.53 (95%CI:0.57, 36.23)	0.21 (95%CI:-0.04, 0.46)
	Remission of proteinuria	5/15	15/17	0.38 (95%CI:0.18,0.79)	-0.55 (95%CI:-0.83, -0.27)
	Side effects causing interruption to treatment	11/15	6/17	2.08 (95%CI:1.02, 4.24)	0.38 (95%CI:0.06, 0.70)
Donadio et al. 1974	Decrease in renal function	1/7	2/8	0.57 (95%CI: 03.06, 5.03)	-0.11 (95%CI:-0.50, 0.29)
	Partial remission	6/9	4/10	1.67 (95%CI:0.69, 4.05)	0.27 (95%CI:-0.17, 0.70)
	Progressed to next stage of renal lesion	5/9	5/8	0.89 (95%CI:0.40, 1.97)	-0.07 (95%CI:-0.54, 0.40)
	leukepenia	5/9	0/8	9.90 (95%CI:0.63, 155.08)	0.56 (95%CI:0.21, 0.90)
Falk et al. 1992	ESRD	4/13	4/13	1.00 (95%CI:0.32, 3.17)	0.00 (95%CI:-0.35, 0.35)
	Glaucoma	0/13	1/13	0.33 (95%CI:0.01, 7.50)	-0.08 (95%CI:-0.27, 0.11)
	Improved / stabilisation of serum Cr	5/13	6/13	0.83 (95%CI:0.34, 2.06)	-0.08 (95%CI:-0.46, 0.30)

Murphy et al. 1992	Mortality	1/19	0/21	3.30 (95%CI:0.14, 76.46)	0.05 (95%CI:-0.08, 0.18)
	Complete remission of nephrotic syndrome	1/13	2/13	0.50 (95%CI:0.05, 4.86)	-0.08 (95%CI: -0.32, 0.17)
	Partial remission of nephrotic syndrome	3/13	7/13	0.43 (95%CI:0.14, 1.30)	-0.31 (95%CI:-0.66, 0.05)
Pahari et al. 1993	Complete remission	33/36	15/35	2.14 (95%CI:1.44, 3.18)	0.49 (95%CI:0.30, 0.68)
	Partial remission	0/36	4/35	0.11 (95%CI:0.01, 1.94)	-0.11 (95%CI: -0.23, 0.00)
	No response	0/36	5/35	0.09 (95%CI:0.01, 1.54)	-0.14 (95%CI:-0.27, -0.02)
	Relapse	2/36	3/35	0.65 (95%CI:0.12, 3.65)	-0.03 (95%CI:-0.15, 0.09)
	Renal function deterioration and ESRF	1/36	5/35	0.19 (95%CI:0.02, 1.58)	-0.12 (95%CI:-0.24, 0.01)
Ponticelli et al. 1998	Side effects causing interruption to treatment	6/50	2/45	2.70 (95%CI:0.57, 12.71)	0.08 (95%CI:-0.03, 0.18)
	Herpes zoster	4/50	0/45	8.12 (95%CI:0.45, 146.71)	0.08 (95%CI:0.00, 0.16)
	Glucose intolerance	1/50	1/45	0.90 (95%CI: 0.06, 13.97)	0.00 (95%CI:-0.06, 0.06)
	Complete remission	12/44	16/43	0.73 (95%CI:0.39, 1.36)	-0.10 (95%CI:-0.29, 0.10)
	Partial remission	24/44	24/43	0.98 (95%CI:0.67, 1.43)	-0.01 (95%CI:-0.22, 0.20)
	Stable	7/44	1/43	6.84 (95%CI:0.88, 53.28)	0.14 (95%CI:0.02, 0.25)
	Worsened	1/44	2/43	0.49 (95%CI:0.05, 5.19)	-0.02 (95%CI:-0.10, 0.05)
Ponticelli et al. 1995	Complete remission	17/42	2/39	7.98 (95%CI: 1.95, 31.97)	0.35 (95%CI:0.19, 0.52)
	Partial remission	9/42	11/39	0.76 (95%CI:0.35, 1.63)	-0.07 (95%CI:-0.26, 0.12)

	Nephrotic syndrome	9/42	6/39	1.39 (95%CI:0.55, 3.55)	0.06 (95%CI:-0.11, 0.23)
	Renal dysfunction	4/42	8/39	0.46 (95%CI:0.15, 1.42)	-0.11 (95%CI:-0.26, 0.04)
	dialysis	2/42	9/39	0.21 (95%CI: 0.05, 0.90)	-0.18 (95%CI:-0.33, -0.04)
	Mortality	1/42	3/39	0.31 (95%CI:0.03, 2.85)	-0.05 (95%CI:-0.15, 0.04)
	Stopped treatment due to side effects	4/42	0/39	8.37 (95%CI: 0.47, 150.62)	0.10 (95%CI: 0.00, 0.19)
Ponticelli et al. 1992	Mortality	1/45	1/47	1.04 (95%CI: 0.07, 16.20)	0.00 (95%CI:-0.06, 0.06)
	Stopped treatment due to side effects	4/45	1/47	4.18 (95%CI:0.49, 35.97)	0.07 (95%CI:-0.03, 0.16)
	Complete remission at end of follow up	14/45	14/47	1.04 (95%CI: 0.56, 1.94)	0.01 (95%CI:-0.17, 0.20)
	Partial remission at end of follow up	10/45	8/47	1.31 (95%CI:0.57, 3.01)	0.05 (95%CI:-0.11, 0.21)
Reichert et al. 1994	Complete remission	1/9	2/9	0.50 (95%CI:0.05, 4.58)	-0.11 (95%CI:-0.45, 0.23)
	Partial remission	3/9	1/9	3.00 (95%CI:0.38, 23.68)	0.22 (95%CI:-0.15, 0.59)
	ESRD*	1/9	4/9	0.25 (95%CI:0.03, 1.82)	-0.33 (95%CI:-0.72, 0.05_
	Mortality	0/9	1/9	0.33 (95%CI:0.02, 7.24)	-0.11 (95%CI: -0.37, 0.15)
	Infectious complication	3/9	0/9	7.00 (95%CI:0.41, 118.69)	0.33 (95%CI:0.01, 0.66)
	Leukopenia	3/9	0/9	7.00 (95%CI:0.41, 118.69)	0.33 (95%CI:0.01, 0.66)
	Nausea and anorexia	3/9	7/9	0.43 (95%CI:0.16, 1.15)	-0.44 (95%CI:-0.86, -0.03)

*ESRD = end-stage renal disease