Pediatr Nephrol (2004) 19:949–955
DOI 10.1007/s00467-004-1553-6

EDITORIAL COMMENTARY

J. H. M. Beimler · K. Andrassy

Cyclophosphamide treatment in systemic necrotizing vasculitis and lupus nephritis. How long? How much?

Received: 12 February 2004 / Revised: 12 May 2004 / Accepted: 12 May 2004 / Published online: 15 July 2004

Abstract The gold standard for inducing remission in systemic necrotizing vasculitis (SNV) and severe lupus nephritis is (and remains) the combination of cyclophosphamide and glucocorticoids. Long-term treatment with cyclophosphamide is limited because of toxicity. Recent prospective studies in antineutrophil cytoplasmic antibody (ANCA)-associated SNV revealed that after achievement of clinical remission (usually within 3–4 months after starting cyclophosphamide) cyclophosphamide can be replaced by azathioprine with no increase in relapse rates if treatment is continued for at least 1 year. Methotrexate is inferior to cyclophosphamide because of increased relapse rates—particularly in those with renal involvement—during follow-up. An ongoing study comparing mycophenolate mofetil (MMF) with azathioprine will clarify whether MMF is as successful as azathioprine or even better. The concomitant use of tumor necrosis factor (TNF)-α blockers increases the efficacy of immunosuppression. TNF-α blockers may be added if SNV is refractory to standard immunosuppressive therapy. However, with this addition to therapy, systemic infections are more frequent. In patients with severe lupus nephritis (WHO IV) the efficacy of combined i.v. therapy with cyclophosphamide and glucocorticoids was shown by NIH trials. This NIH regimen competes with the EURO-Lupus nephritis schedule with a lower dose of i.v. cyclophosphamide followed by maintenance therapy with azathioprine. Long-term follow-up is, however, still lacking in the EURO-Lupus trial. Ongoing prospective studies will reveal whether cyclophosphamide may be substituted by MMF from the very beginning or whether MMF is superior to azathioprine during maintenance therapy of lupus nephritis.

J. H. M. Beimler (✉) · K. Andrassy
Division of Nephrology, Department of Medicine,
University Hospital Heidelberg,
Bergheimerstrasse 56a, 69115 Heidelberg, Germany
e-mail: beimler@gmx.de
Tel.: +49-6221-5635289
Fax: +49-6221-911279

Keywords Systemic necrotizing vasculitis · Lupus nephritis · Cyclophosphamide · Azathioprine · Mycophenolate mofetil

Introduction

The modern therapy of vasculitis started in the late 1940s with the use of corticosteroids. In the late 1960s, Fauci and Wolff [1], at the National Institutes of Health (NIH), began to use low-dose, daily cyclophosphamide in combination with prednisone to treat patients with generalized Wegener granulomatosis (WG). Although this combination therapy showed clear efficacy, long-term treatment with cyclophosphamide to prevent disease relapse was not feasible because of cumulative drug toxicity. In the last decade new immunosuppressive agents were introduced into vasculitis therapy to reduce and minimize toxicity and improve efficacy. Some of these drugs might have the potential to replace or complement the conventional combination therapy.

Cyclophosphamide: toxicity and its prevention

In 1958 the cytotoxic drug cyclophosphamide was synthetized by Arnold and Borseaux [2] and was first introduced as an alkylating agent in cancer therapy. Cyclophosphamide prevents cell division primarily by cross-linking DNA strands and is cytotoxic for T- and B-lymphocytes. After oral administration, cyclophosphamide is well absorbed with a bioavailability of 75%–100%. There are no main pharmacokinetic differences between oral and parenteral administration. Cyclophosphamide and its metabolites are excreted by the kidneys; the half-life is quite variable, about 6.5 h in adults (range 1.8–12.4 h) and 4.1 h in children (range 2.4–6.5 h) [3], and increases with renal insufficiency.

The toxic effects of cyclophosphamide often depend on the frequency of administration and the cumulative administered dose. The well-known side effects of cy-

clophosphamide therapy include myelosuppression, nausea and vomiting, hemorrhagic cystitis, secondary malignancies, and infertility. The major dose-limiting effect of cyclophosphamide is myelosuppression with neutropenia and thrombocytopenia. The leukocyte nadir is reached within 7–14 days of administration of cyclophosphamide. The incidence of severe infections almost doubled (from approximately 10% to 20%) with the addition of cyclophosphamide to the vasculitis therapy [4]. One of the most common opportunistic infections in patients with cytotoxic therapy is *Pneumocystis carinii* pneumonia. Prophylaxis with low-dose trimethoprim-sulfamethoxazole (TMZ) should be considered in all patients receiving cyclophosphamide and high-dose glucocorticoid therapy [5]. If advanced renal insufficiency is present, the myelosuppressive effect can be prolonged. If leukocyte counts fall below 4.0×10^6 cells/l, frequent dose adjustments are necessary to prevent such decreases. Dose-related cyclophosphamide-induced hemorrhagic cystitis is due to the contact of active and toxic metabolites (acrolein) in the urine with the bladder mucosa. Hemorrhagic cystitis occurs in about 10% of patients and may occur during or several months after treatment. The risk of hemorrhagic cystitis can be minimized by sufficient hydration to reduce the direct urotoxicity. With intermittent therapy with higher doses of cyclophosphamide, patients can be hydrated intravenously; another option is the co-administration of 2-mercaptoethansulfonate (MESNA), which binds and inactivates acrolein. MESNA and hyperhydration seem to be equally effective in preventing hemorrhagic cystitis. The administration of MESNA is recommended only for high-dose therapy >1,000 mg/m^2. According to Talar-Williams et al. [6], the estimated incidence of transitional cell carcinoma of the bladder 15 years after the first exposure to cyclophosphamide is about 16%. The risk for bladder cancer should be considered lifelong because transitional cell carcinoma of the bladder was reported as late as 17 years after discontinuation of cyclophosphamide therapy. In addition to transitional cell carcinoma of the bladder, cyclophosphamide therapy has been dose-dependently associated with a higher risk of developing myelodysplasia and acute myeloid leukemia, lymphoma, or skin cancer.

Cyclophosphamide can damage the germinal epithelium in men and therefore inhibit spermatogenesis; in women, sterility can develop due to premature ovarian failure (POF). The impairment of gonadal function after cytotoxic therapy is much more frequent in men than in women, occurring in up to 90% of post-pubertal males. In patients with lupus nephritis, POF was reported in half of all treated women after cyclophosphamide pulse therapy, affecting 100% of those older than 30 years, about 50% between 20 and 30 years, and only 13% of patients younger than 20 years of age. The dose limit for gonadal toxicity is between 150 and 250 mg/kg. If the cumulative dose of cyclophosphamide exceeds 50 g, sterility develops. In men, sperm-banking prior to treatment is the only possible means of preserving fertility. Because dividing cells are more sensitive to the cytotoxic effects of alkylating chemotherapy, inhibition of the pituitary-gonadal axis by gonadotropin-releasing hormone (GnRH) agonists may render the germinal epithelium less susceptible to the cytotoxic effects of chemotherapy. GnRH analogues have been shown to inhibit chemotherapy-induced ovarian follicular depletion in the rat. Preliminary data on the administration of GnRH analogues in parallel with chemotherapy in patients with malignant lymphoma or systemic lupus erythematosus (SLE) are encouraging. The temporary induction of a prepubertal hormonal milieu with the monthly injection of a GnRH analogue during cyclophosphamide therapy significantly decreases the risk of POF [7].

Cyclophosphamide is considered to be teratogenic and fetotoxic, and is contraindicated during pregnancy due to the risk of congenital malformations. Contraception is recommended for at least 4 months post therapy. Other less frequent side effects of cyclophosphamide therapy include hypersensitivity, pulmonary fibrosis, cardiomyopathy, and the development of SIADH (syndrome of inappropriate secretion of ADH).

Cyclophosphamide treatment protocols in systemic necrotizing vasculitis

In 50%–75% of cases primary systemic necrotizing vasculitis (SNV) is associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA). ANCA-associated systemic vasculitis is characterized by a vasculitis predominantly involving small vessels. The category of small vessel vasculitis includes WG, microscopic polyangiitis (MPA), and Churg-Strauss angiitis. A specificity of >90% has been demonstrated for the diagnosis of ANCA-associated systemic vasculitis [8]. In ANCA-associated systemic vasculitis, renal involvement is common and characterized by a focal, necrotizing, crescentic glomerulonephritis without or with only a few immune deposits (pauci-immune). According to a review of renal histology in the European Vasculitis Study Group (EUVAS) clinical trials, only minor quantitative but not qualitative differences between MPA and WG were found [9]. In order to develop therapeutic regimens based on the disease severity at presentation, the interdisciplinary EUVAS introduced a categorization of patients with ANCA-associated systemic vasculitis according to disease severity and activity at diagnosis.

Wegener granulomatosis

In generalized WG and MPA, cyclophosphamide therapy is well established. The mean survival time of untreated patients with WG is about 5 months; more than 90% of untreated patients die within 2 years of diagnosis. Glucocorticoid therapy is effective in reducing the inflammatory symptoms of WG, but as a single therapy is not able to control the disease in the long term. A prospective trial with observation times as long as 25 years estab-

lished the efficacy of cyclophosphamide and steroids in WG [10]. This combination therapy, consisting of prednisone 1 mg/kg per day and oral cyclophosphamide 2 mg/kg per day (Fauci-scheme) is still in use in clinical practice. Dose reductions of cyclophosphamide are recommended to prevent leukopenia and to maintain the leukocyte count above 3.0×10^6 cells/l. Usually prednisone is tapered as soon as disease activity is under control; cyclophosphamide therapy is continued until at least 1 year after clinical remission. In the EUVAS trials, cyclophosphamide 2 mg/kg per day was given for 3 months to a maximum of 6 months until remission occurred. After remission the cyclophosphamide dose was reduced to 1.5 mg/kg per day. Complete remission was shown in 75% of the followed patients and the systemic disease markedly improved in as many as 91%. In the long-term follow-up 11% of patients died of active WG and 49% of patients who achieved remission had at least one relapse of the disease.

Despite the proven efficacy of cyclophosphamide therapy, cumulative drug toxicity with long-term treatment is a limiting factor. As repeated courses of cyclophosphamide to prevent disease relapses are associated with a high drug-related morbidity and mortality, alternative immunosuppressive regimens for the treatment of WG are under investigation. Treatment with high-dose monthly pulses of cyclophosphamide is less toxic than daily low-dose therapy. According to earlier experiences with lupus nephritis, the efficacy of i.v. pulses of cyclophosphamide in 4-weekly dosing intervals was investigated in several smaller studies. A meta-analysis of three randomized trials comparing daily oral cyclophosphamide with i.v. pulse therapy showed no differences in mortality and renal survival, but a higher relapse rate with i.v. therapy and more adverse events following daily oral treatment [11]. A recent study of the French Co-operative Study Group showed that in patients with polyarteritis and MPA 12 monthly pulses of cyclophosphamide are superior to 6 monthly pulses with respect to remission and disease relapses [12]. In a consensus protocol the EUVAS group designed a treatment regimen for ANCA-associated vasculitis with ten pulses of cyclophosphamide (15–20 mg/kg i.v.) over 6 months, starting with 2-week intervals for the first three pulses then switching to 3-week intervals. Currently a randomized trial, CYCLOPS, comparing this regimen with daily oral cyclophosphamide is in progress [13]. Alternative regimens with i.v. pulses of cyclophosphamide include an accelerated high-dose course of six pulses, especially in resistant cases. Another option is an initial therapy with pulses of cyclophosphamide in 2- to 4-week intervals, to avoid overimmunosuppression, followed by intensive oral cyclophosphamide therapy or azathioprine, depending on disease severity and clinical course [14].

Combination therapy with glucocorticoids and cyclophosphamide is mandatory only in systemic WG with major organ involvement. In localized disease, such as isolated sinus disease or subglottic stenosis, cytotoxic drug therapy is usually not required.

Microscopic polyangiitis

MPA is a primary systemic vasculitis and belongs, like WG and Churg-Strauss angiitis, to the category of ANCA-associated vasculitis. As in WG, treatment of MPA is based on a combination therapy of glucocorticoids and cyclophosphamide. A recent study by Jayne et al. [15] found no difference in remission rates between the two disease entities. In this study patients with MPA showed a significantly lower relapse rate than patients with WG.

Other systemic vasculitides

In other systemic vasculitides such as polyarteritis nodosa, Churg-Strauss syndrome, Takayasu arteritis, essential mixed cryoglobulinemia, or Henloch-Schönlein purpura, cyclophosphamide has been used with variable success. Due to the rareness of these diseases, available data are not sufficient to give detailed recommendations. The use of cyclophosphamide with or without glucocorticoids must be based on the individual course of the disease. Particularly in progressive disease, patients may benefit from cyclophosphamide therapy. Patients with Churg-Strauss syndrome may need cyclophosphamide therapy in life-threatening situations with cardiac involvement for induction of remission. In Churg-Strauss syndrome and polyarteritis nodosa with good prognosis, i.v. pulse therapy and oral cyclophosphamide therapy seem to be equally effective [16].

Alternative therapeutic strategies in ANCA-associated vasculitis

In analogy to the treatment of rheumatoid arthritis and in an attempt to avoid toxicity of cyclophosphamide therapy, low-dose methotrexate (MTX) has been used for selected patients with ANCA-associated vasculitis. Remission rates of 50%–70% have been reported for combination therapy of MTX and glucocorticoids in WG. In the NORAM trial by the EUVAS group (submitted) oral MTX was given in doses between 15 and 25 mg/week for the 1st year after diagnosis compared with a standard regimen with oral cyclophosphamide at doses of 2 mg/kg per day. Both groups received oral prednisolone at 1 mg/kg per day tapered over the 1st year. At 6 months the remission rate with oral MTX/prednisolone was equivalent to the standard combination therapy (89.8% vs. 93.5%) and MTX/prednisone was well tolerated. The high number of relapses after termination of MTX (69.5% vs. 44.2%) suggests the need for continuation of immunosuppression after 12 months. These findings are not supported by the observations of Reinhold-Keller et al. [17]. They examined the long-term-efficacy of low-dose i.v. MTX with and without concomitant glucocorticoids for maintenance of remission in patients with generalized WG after induction of remission with cyclophosphamide and steroids.

MTX was well tolerated; however, one-third of patients (36.6%) relapsed during ongoing treatment with MTX. Although long-term tolerability of MTX has been shown, serious side effects such as bone marrow and lung toxicity, secondary malignancies, and teratogenicity must be taken into consideration.

In order to maintain remission after initial cyclophosphamide therapy, azathioprine has successfully been used as maintenance therapy. In 2003, results of the CYCAZAREM trial, a prospective, controlled randomized study investigating the effectiveness of azathioprine as maintenance therapy in 158 patients with ANCA-associated vasculitis, were published. After induction of remission with daily oral cyclophosphamide and prednisolone, azathioprine at 2 mg/kg per day was compared with oral cyclophosphamide at 1.5 mg/kg per day. After 18 months the trial showed no difference in relapse rates when oral cyclophosphamide was replaced by azathioprine (azathioprine 15.5% vs. cyclophosphamide 13.7%, P =0.65). In the same study patients with WG showed a significantly higher relapse rate than patients with MPA. Two ongoing trials of the EUVAS group are currently investigating the use of azathioprine as maintenance therapy of ANCA-associated vasculitis. The REMAIN trial is comparing the effectiveness of long-term azathioprine therapy over 42 months with an azathioprine regimen with a 21-month duration. With a maintenance regimen over 48 months the IMPROVE study is comparing mycophenolate mofetil (MMF) with azathioprine. With the idea of ongoing infection as an underlying promoter of vasculitis, antibiotic therapy with TMZ to induce and maintain remission was investigated. In localized disease, e.g., isolated sinus disease, but not in generalized ANCA-associated vasculitis, TMZ can stabilize disease activity, but is not able to induce long-term remission. Stegeman et al. [18] showed that in WG TMZ (2×960 mg/day) can prolong the duration of remission after achieving remission with cyclophosphamide. In the TMZ group they found fewer respiratory tract infections and relapses. The authors attributed this effect to a better control of respiratory tract infections with *Staphylococcus aureus* and also suggested the use of a topic antibiotic ointment (mupirocin). Patients initially presenting with rapid progressive glomerulonephritis and severe acute renal failure (serum creatinine >500 μmol/l) have the highest risk of death and end-stage renal failure.

The majority of non-randomized studies could not show any additional benefit of plasma exchange therapy in patients with severe vasculitis. A randomized trial with polyarteritis nodosa and Churg-Strauss syndrome was negative. There is, however, growing evidence for a possible role of plasma exchange therapy in patients with severe renal vasculitis. The MEPEX trial [19] compared plasma exchange (7×60 ml/kg per 2 weeks) with methylprednisolone pulse therapy (15 mg/kg per day over 3 days) in addition to standard therapy with cyclophosphamide and prednisolone. Mortality was high in both groups (25%); in patients with oliguria at presentation plasmapheresis resulted in a significantly higher number of patients not requiring permanent dialysis.

In a small group of patients with refractory disease an anti-T-cell-directed treatment with antithymocyte globulin (ATG) may be a therapeutic option. Using a standardized regimen of ATG in a small, uncontrolled study, the investigators [20] were able to induce remission in 13 of 15 patients. Although further immunosuppressive treatment was required, a less-intensive regimen could be used in most patients.

Limited data are available for the use of i.v. immunoglobulins in systemic vasculitis. There may be a role for i.v. immunoglobulins as an additional therapeutic agent in relapsing or refractory disease.

Systemic lupus erythematosus

Up to two-thirds of patients with SLE develop renal disease at any stage of their illness. Renal involvement ranges from asymptomatic proteinuria to rapidly progressive crescentic glomerulonephritis. Diffuse proliferative glomerulonephritis (WHO class IV) carries the risk of developing end-stage renal failure at 5 years in up to 48% of patients [21]. In severe lupus nephritis cyclophosphamide has proven its efficacy in preserving long-term renal function. Several randomized controlled trials at the NIH have evaluated the use of cyclophosphamide, given as intermittent i.v. pulses or orally, in combination with corticosteroids. According to these trials the majority of patients with proliferative lupus nephritis have been treated with long-term, high-dose i.v. cyclophosphamide pulses, combined with glucocorticoids (NIH regimen). The NIH regimen includes monthly i.v. pulses of cyclophosphamide 0.75–1.0 g/m^2 per month over the first 6 months followed by 3-monthly pulses up to 30 months. The NIH trials have demonstrated the superiority, in terms of achieving remission [22] and long-term prognosis [23], of a combined regimen with cyclophosphamide and glucocorticoids compared with glucocorticoids alone. It remains unclear whether i.v. pulse or daily oral cyclophosphamide therapy is more efficacious in lupus nephritis. In the NIH trials the intermittent i.v. cyclophosphamide regimen seemed to be more effective in preserving long-term renal function and was associated with fewer side effects such as cystitis and amenorrhea. However, a recent trial [24] showed a higher remission rate and fewer renal relapses with the oral cyclophosphamide regimen at an observation time of 24 months. However, the high-dose cyclophosphamide regimen carries a higher risk of side effects such as severe infections, ovarian failure, and malignancies.

As an alternative to the extended high-dose course of cyclophosphamide in the NIH regimen, the Euro-Lupus Nephritis trial [25] compared a high- and a low-dose i.v. cyclophosphamide regimen as remission-inducing therapy for proliferative lupus nephritis. With both regimens azathioprine (2 mg/kg per day) was used as maintenance therapy after discontinuation of cyclophosphamide. The

high-dose group received six monthly pulses and two quarterly pulses with standard doses, the low-dose group six fortnightly pulses of 500 mg i.v. cyclophosphamide providing a cumulative dose of 3 g. There were no significantly different treatment effects in the two groups. The initial response to therapy and the rate of achieving remission were similar and the number of renal flares did not differ with the two regimens. Fewer severe infections occurred in the low-dose group, but this was not statistically significant. These results question the current practice of treating all patients with lupus nephritis with an extended high-dose cyclophosphamide therapy based on the NIH trials. However, several important differences between the NIH trials and the Euro-Lupus Nephritis trial must be emphasized. Most patients in the European trial had relatively mild renal disease and few black or African-Caribbean patients with poorer prognosis were included. Finally, the follow-up period of the NIH trials and therefore the cumulative dose of cyclophosphamide was longer compared with the European trial. The Euro-Lupus Nephritis trial suggests a cyclophosphamide induction regimen with shorter duration and lower doses followed by azathioprine maintenace therapy as an effective treatment for lupus nephritis with reduced toxicity. As in ANCA-associated vasculitis the optimal maintenance therapy after induction of remission with cyclophosphamide remains a critical issue. Long-term azathioprine therapy after induction therapy with cyclophosphamide has proven its efficacy in preventing renal relapses, but in the Euro-Lupus Nephritis trial 25% of patients experienced at least one renal flare while on azathioprine therapy.

A new immunosuppressive agent, increasingly used in SLE, is MMF. A study in Chinese lupus patients with proliferative lupus nephritis [26] showed its short-time efficacy given together with high-dose glucocorticoids. The ongoing MAINTAIN study, launched by the European Working Party on Systemic Lupus Erythematosus, is evaluating the efficacy of MMF compared with azathioprine for maintenance of remission of proliferative lupus nephritis after a short course of i.v. low-dose cyclophosphamide induction therapy. In a recent study Contreras et al. [27] reported a prospective controlled trial comparing three maintenance regimens after induction therapy with i.v. cyclophosphamide: quarterly i.v. pulses of cyclophosphamide, oral MMF, and oral azathioprine. There were no differences in renal survival, but event-free survival (composite endpoint of death and renal failure) was significantly better in both the azathioprine and MMF groups. These results emphasize that azathioprine and MMF are good options for maintenance therapy in proliferative lupus nephritis. The authors' conclusion that for maintenance therapy both azathioprine and MMF are superior to cyclophosphamide in terms of efficacy and safety needs to be confirmed in further studies with longer follow-up and a representative population of patients.

Newer immunosuppressive therapies

In smaller open-label studies of selected patients, especially those with refractory disease, alternative immunosuppressive agents have been shown to be effective in the therapy of SNV. In the past, treatment with polyclonal or monoclonal T-cell-depleting antibodies has proven its efficacy in refractory disease, but long-term toxicity limits their use. As in other autoimmune disease, in systemic vasculitis the monoclonal anti-CD20 antibody rituximab, a B-cell-depleting agent, has been used with success in single cases. More recent data support the therapeutic role of tumor necrosis factor (TNF)-α antagonists such as etanercept or infliximab. Several clinical and in vitro studies have demonstrated an important role for TNF-α in granuloma formation and the development of small vessel vasculitis. The blockade of TNF-α is efficient in the treatment of different chronic inflammatory disorders such as rheumatoid arthritis. Lamprecht et al. [28] investigated the effectiveness of TNF-α blockade with the chimeric monoclonal anti-TNF-α antibody infliximab in six patients with WG refractory to standard treatment. Patients received infliximab in 2- to 4-week intervals until achieving remission at doses between 3 and 5 mg/kg. Remission was induced in five patients and corticosteroid doses could be tapered. The soluble TNF-α receptor etanercept was shown to be safe and effective in patients receiving conventional treatment for WG [29]. Enrollment for a randomized trial, the Wegener's Granulomatosis Etanercept Trial (WGET), was completed in 2002. These first data suggest that TNF-α blockade may provide an effective therapeutic option in the treatment of active WG refractory to standard treatment with cyclophosphamide and corticosteroids.

Conclusions

Systemic vasculitis, particularly ANCA-associated vasculitis, can present as life-threatening disease in which cyclophosphamide therapy and glucocorticoids are highly effective. This combination therapy still represents the gold standard for inducing remission in systemic vasculitis and results in long-term survival. High-dose monthly pulses are less toxic than daily oral low-dose therapy, but the relapse rates with i.v. therapy are higher. The combination of an initial therapy with 2- to 4-week pulses of cyclophosphamide, followed by intensive oral cyclophosphamide treatment until remission is achieved, is presently our treatment of choice. When therapy is tapered and discontinued, however, disease relapses are common. Although cyclophosphamide treatment is effective in managing these relapses, long-term use is limited because of toxicity. There are still concerns about whether reduced cyclophosphamide therapy could result in a higher rate of relapses during long-term observation. After achievement of clinical remission, which is usually attained 3–4 months after induction therapy with cyclophosphamide, alternative immunosuppressive agents such

as azathioprine or MMF may replace cyclophosphamide for long-term maintenance therapy. New approaches to treatment that further reduce the risk of toxic effects of cyclophosphamide and the risk of relapse in patients with ANCA-associated vasculitis are mandatory. The safety and efficacy of immunomodulatory agents directly targeting components of the immune response, such as TNF-α blockade or lymphocyte depletion, are currently under investigation in patients with vasculitides. They are promising even in patients with refractory disease. In patients with severe lupus nephritis (WHO IV) the NIH regimen competes with the EURO-Lupus Nephritis schedule with a lower dose of i.v. cyclophosphamide followed by a maintenance therapy with azathioprine. However, long-term follow-up data and the consequences for relapsing disease are still lacking in the EURO-Lupus trial. Ongoing prospective studies will clarify whether cyclophosphamide may be substituted by high-dose MMF (3 g/day) as induction therapy or whether MMF is superior to azathioprine during maintenance therapy of lupus nephritis.

References

1. Fauci AS, Wolff SM (1973) Wegener's granulomatosis, studies in 18 patients and a review of the literature. Medicine (Baltimore) 52:535–561
2. Arnold H, Borseaux F (1958) Synthese und Abbau cytostatisch wirksamer cyclischer N-Phosphoamidester des Bis-(beta-chloräthyl)-amins. Angew Chemie 70:539–544
3. Grochow LB, Colvin M (1979) Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet 4:380–394
4. Gayraud M, Guillevin L, Le Toumelin P, Cohen P, Lhote F, Cassasus P, Jarrousse B, French Vasculitis Study Group (2001) Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 44:666–675
5. Ognibene FP, Shelhamer JH, Hoffman GS, Kerr GS, Reda D, Fauci AS, Leavitt RY (1995) *Pneumocystis carinii* pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. Am J Respir Crit Care Med 151:795–799
6. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, Hoffman GS, Fauci AS, Sneller S (1996) Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 124:477–484
7. Blumenfeld Z, Dann E, Avivi I, Epelbaum R, Rowe JM (2002) Fertility after treatment for Hodgkin's disease. Ann Oncol 13 [Suppl 1]:138–147
8. Hagen EC, Andrassy K, Csernok E, Daha MR, Gaskin G, Gross WL, Hansen B, Heigl Z, Hermans J, Jayne D, Kallenberg CG, Lesavre P, Lockwood CM, Ludemann J, Mascart-Lemone F, Mirapeix E, Pusey CD, Rasmussen N, Sinico RA, Tzioufas A, Wieslander J, Wiik A, Van der Woude FJ (1996) Development and standardization of solid phase assays for the detection of anti-neutrophil cytoplasmic antibodies (ANCA): a report on the second phase of an international cooperative study on the standardization of ANCA assays. J Immunol Methods 196:1–15
9. Hauer HA, Bajema IM, Houwelingen HC van, Ferrario F, Noel LH, Waldherr R, Jayne DR, Rasmussen N, Bruijn JA, Hagen EC; European Vasculitis Study Group (EUVAS) (2002) Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups. Kidney Int 61:80–89
10. Hoffmann GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS (1992) Wegener granulomatosis, an analysis of 158 patients. Ann Intern Med 116:488–498
11. De Groot K, Adu D, Savage C (2001) The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. Nephrol Dial Transplant 16:2018–2027
12. Guillevin L, Cohen P, Mahr A, Arene JP, Mouthon L, Puechal X, Pertuiset E, Gilson B, Hamidou M, Lanoux P, Bruet A, Ruivard M, Vanhille P, Cordier JF (2003) Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. Arthritis Rheum 49:93–100
13. Jayne DR, Rasmussen N (1997) Treatment of anti-neutrophil cytoplasm autoantibody associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. Mayo Clin Proc 72:737–747
14. Andrassy K, Erb A, Koderisch J, Waldherr R, Ritz E (1991) Wegener granulomatosis with renal involvement: patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. Clin Nephrol 35:139–147
15. Jayne D, Rasmussen N, Andrassy K, Bacon P, Cohen Tervaert JW, Dadoniene J, Ekstrand A, Gaskin G, Gregorini G, Groot K de, Gross W, Hagen EC, Mirapeix E, Pettersson E, Siegert C, Sinico A, Tesar V, Westman K, Pusey C; European Vasculitis Study Group (2003) A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44
16. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, Godeau B, Ruel M, Vidal E, Piontud M, Ducroix JP, Lassoued S, Christoforov B, Babinet P (1997) Treatment of good prognosis polyarteritis nodosa and Churg-Strauss-syndrome: comparison of steroids and two cyclophosphamide regimens in 25 patients. Br J Rheumatol 36:1290–1297
17. Reinhold-Keller E, Fink C, Herlyn K, Gross WL, Groot K de (2002) High rate of renal relapse in 71 patients with Wegener granulomatosis under maintenance of remission with low-dose methotrexate. Arthritis Rheum 47:326–332
18. Stegeman CA, Cohen Tervaert JW, Jong PE de, Kallenberg CG (1996) Trimethoprim-sulfamethaxozole (co-trimoxazole) for the prevention of relapse of Wegener granulomatosis. N Engl J Med 335:16–20
19. Gaskin G, Jayne DRW (2002) Adjunctive plasma exchange is superior to methylprednisolone in acute renal failure due to ANCA-associated glomerulonephritis. J Am Soc Nephrol 13:F-FC-010
20. Schmitt WH, Hagen EC, Neumann I, Nowack R, Flores-Suarez LF, Woude FJ van der; for the European Vasculitis Study Group (2004) Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. Kidney Int 65:1440–1448
21. Cameron JS (1999) Lupus nephritis. J Am Soc Nephrol 10:413–424
22. Gourley MF, Austin HA III, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD (1996) Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. Ann Intern Med 125:549–557
23. Boumpas DT, Austin HA III, Vaughan EM, Klippel JH, Steinberg AD, Yarboro CH, Balow JE (1992) Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 340:741–745
24. Mok CC, Ho CTK, Siu YP, Chan KW, Kwan TH, Lau CS, Wong RW, Au TC (2001) Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. Am J Kidney Dis 38:256–264
25. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido ER, Danieli MG, Abramovicz D, Blockmans D, Mathieu A, Direskeneli H, Galeazzi M, Gul A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font J, Depresseux G, Cosyns JP, Cervera R (2002) Immunosuppres-

sive therapy in lupus nephritis. The Euro-Lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 46:2121–2131
26. Chan TM, Li FK, Tang CS, Wong RWS, Fang GX, Ji YL, Lau CS, Wong AK, Tong MK, Chan KW, Lai KN (2000) Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med 343:1156–1162
27. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D (2004) Sequential therapies for proliferative lupus nephritis. N Engl J Med 350:971–980
28. Lamprecht P, Voswinkel J, Lielienthal T, Nolle B, Heller M, Gross WL, Gause A (2002) Effectiveness of TNF-α blockade with infliximab in refractory Wegener granulomatosis. Rheumatology 41:1303–1307
29. Stone JH (2003) Current status of tumor necrosis factor inhibition strategies in the treatment of vasculitis. Kidney Blood Press Res 26:240–248