

M. Haubitz

## Acute and Long-term Toxicity of Cyclophosphamide

Cyclophosphamid has been widely used in patients with kidney diseases such as vasculitis, SLE, steroid-resistant nephrotic syndrome and also progressive IgA-nephropathy. Beside acute side effects like bone-marrow toxicity, infections, haemorrhagic cystitis, gastrointestinal side effects and hair loss, the main concern is the long-term effect of the drug which may occur years after treatment when patients with end-stage renal disease have received a transplant. Incidences increase for tumours, especially bladder carcinoma, lymphomas and tumours of the skin, for the myelodysplastic syndrome and the permanent infertility.

As most of the side effects are associated with the total dose of CP, dose reduction by stage-adapted treatment, i.v. administration, shorter treatment time and prevention of relapses is an important issue. In addition, some side effects may be reduced or even prevented, e.g. bladder toxicity by the use of Mesna, skin tumours by sun blockers, permanent infertility by sperm conservation or by gonadotropin-releasing hormone analogue. In patients with high CP exposure awareness of the increased tumour risk may lead to early detection and the chance of curative treatment.

### Key words:

cyclophosphamide, toxicity, opportunistic infection, risk of tumours, infertility, MDS

### *Akute Nebenwirkung und Langzeittoxizität von Cyclophosphamid*

*Cyclophosphamid wird in der Nephrologie bei einer Vielzahl von Erkrankungen eingesetzt. So spielt es bei der Therapie der SLE und der systemischen Vaskulitiden eine entscheidende Rolle. Auch beispielsweise das steroidresistente nephrotische Syndrom und möglicherweise auch die rasch progrediente IgA-Nephropathie stellen eine Indikation dar.*

*Neben den während der Therapie zu beobachtenden Nebenwirkungen, wie der Knochenmarkstoxizität, der vermehrten Anfälligkeit für Infekte, der hämorrhagischen Zystitis, den gastrointestinalen Nebenwirkungen und dem Haarausfall, spielt vor allem die Langzeittoxizität eine wichtige Rolle. Die Auswirkungen kommen oft erst nach Jahren zum Tragen, wenn der Patient beispielsweise bereits nierentransplantiert ist. Hier ist neben der Erhöhung des Tumorrisikos (vor allem für Blasenkarzinom, Hauttumore und Lymphome) die Entwicklung eines myelodysplastischen Syndroms und bei jungen Patienten die Infertilität zu nennen.*

Department of Nephrology, Medical School Hannover

Da die meisten Nebenwirkungen dosisabhängig auftreten, kommt der Reduktion der Cyclophosphamidgesamtosis eine entscheidende Bedeutung zu. Neben einer engen Indikationsstellung für Cyclophosphamid (z.B. stadienadaptierte Therapie bei granulomatöser ANCA-assoziiertes Vasculitis) und der i.v. Gabe zur Dosisreduktion, spielt die verkürzte Therapiedauer mit Cyclophosphamid und eine remissionserhaltende Therapie zur Vermeidung einer Retherapie eine wichtige Rolle. Darüber hinaus sind einige Nebenwirkungen vermeidbar oder in ihrer Inzidenz zu reduzieren, wie zum Beispiel die Blasentoxizität durch die Applikation von Mesna, das Risiko von Hauttumoren durch Sonnenschutz oder die Infertilität durch eine Spermienkonservierung bzw. möglicherweise durch die Gabe eines Gonadotropin-Releasing-Hormon-Analogen. So sollte schon vor der Gabe von Cyclophosphamid alles getan werden, um Spät komplikationen zu vermeiden. Bei Patienten mit hoher Cyclophosphamiddosis können Vorsorgeuntersuchungen wie regelmäßige Hautinspektionen und Blasenspiegelungen zu einer frühen Tumorerkennung mit der Chance einer kurativen Therapie führen.

#### Schlüsselwörter:

Cyclophosphamid, Toxizität, opportunistische Infektion, Tumorrisiko, Infertilität, MDS

Cyclophosphamide was first synthesized in 1958 by Arnold, Bourseaux and Brock (Figure 1). It is an alkylating agent with an active metabolite leading to DNA cross-linking. In patients with autoimmune and kidney diseases the career of this drug began when Fauci decided to use it in patients with Wegener's granulomatosis. Before his regimen, still known as the "Fauci protocol", patients were treated with steroids alone and had a median survival of 12.5 months [1]. Adding azathioprine or chlorambucil had only a marginal impact on mortality but the treatment with oral CP together with steroids gave more than 90 % of the patients the chance of long-term survival [2]. Since then CP has been used for many renal diseases and is still given to most patients with proliferative lupus nephritis [3,4] and ANCA-associated systemic vasculitis [5,6], Goodpasture syndrome and patients with other systemic vasculitides [7]. In addition, CP is administered to patients with steroid resistant nephrotic syndrome due to minimal change nephropathy or focal segmental glomerulosclerosis, to patients with membranous nephropathy, progressive

IgA-nephropathy and others [7-10].

Initially the major concerns were the severe side effects of the drug during treatment, mainly bone marrow toxicity and severe infections, but in the last decade long-term toxicity has gained more and more attention. Serious life-threatening side effects may occur after years when the patient has developed end-stage renal disease and is on dialysis or has received a renal transplant. In the following I will summarize the acute and chronic side effects of CP, and then concentrate on the prevention and early detection of its toxicity.

## Acute Toxicity

The side effects of CP are well known in patients receiving the drug for the treatment of solid tumours, lymphomas, leukaemias or for conditioning before stem cell or bone marrow transplantation. Bone marrow toxicity with opportunistic infections, haemorrhagic cystitis, temporary infertility, nausea, vomiting and hair loss are seen frequently whereas pneumonitis, liver or cardiac toxicity are rare. Patients treated for vasculitis, proliferative lupus nephritis or other renal diseases had a comparable spectrum of side effects but with clearly lower incidence and severity due to the lower dose. The main concern in these patient groups is the occurrence of severe infections with a significantly rising incidence with increasing age of the patients. A patient with an ANCA-associated vasculitis aged 65 years has a 50 % chance of developing a severe infection, defined by admission to the hospital and intravenous drug administration. The risk further increases to about 70 % at the age of 70 years. The spectrum of infections is wide, including not only bacterial infections like pneumonia, endocarditis, spondylodiscitis and Staphylococcus aureus sepsis with a catheter as origin, but also viral and fungal infections. Thus, beside the use of cotrimoxazol to prevent Pneumocystis jiroveci pneumonia, recommendations for prophylaxis are hard to give.

Although the entire urinary tract is at risk of toxicity from the metabolite of CP, acrolein, the bladder is most susceptible because of its prolonged exposure. Nevertheless, haemorrhagic cystitis is relatively rare in our nephrologic patient group even if sodium 2-mercaptoethane sulphonate (mesna), a substance that inactivates acrolein, is not used. This is mainly due to fluid administration in patients with intravenous CP

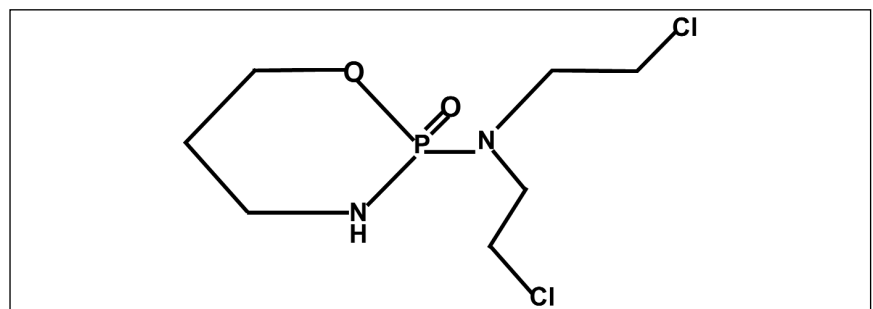


Fig. 1: Chemical structure of cyclophosphamide

treatment and to a relatively low daily dose in orally treated patients. Other groups have reported an incidence of 12 % or even 29 % in patients with Wegener's granulomatosis [11,12]. As serious allergic reactions to mesna are rarely seen [13], the benefit clearly outweighs the risk in these patient groups too. However, the relation of CP-induced cystitis and the development of bladder cancer have not been defined and up to now there are no data showing that the risk of a bladder carcinoma can be reduced by the use of mesna.

### Chronic Toxicity

The main concerns regarding CP administration are the increased risk of tumours, of the myelodysplastic syndrome (MDS) and gonadal toxicity. Cyclophosphamide has been shown to increase the incidence of malignancies e.g. of the bladder, the haematopoietic system and the skin. There is a 1.6- to 2.4-fold overall increase in malignancies [14,15], depending on the total CP dose and the time of follow-up. For skin cancer the risk increases up to 10.4-fold [14], for lymphomas up to 11-fold [15] and for leukaemia up to 5.7-fold [16]. Regarding bladder carcinoma, the incidence varies between less than 1 % [11], 3 % [14,15] and 5 % [12] corresponding to a 5- to 33-fold increase. The risk rises with the total CP dose administered and the follow-up, and an incidence of 16 % has been reported after 15 years [12]. It is difficult to pinpoint a critical dose. The data of Baker et al. in patients with rheumatoid arthritis showed increasing numbers of malignancies, especially of the bladder, in a group of patients with more than 70 g CP and a follow-up time of more than 8 years [17]. Episodes of non-glomerular microhaematuria are a risk factor for the development of bladder cancer [12] and occur more often in smokers. However, microhaematuria is not a reliable marker as these episodes were not always frequent and recurrent. Cytologic urine examination is of limited usefulness in monitoring patients at risk as it is relatively insensitive for the detection of low-grade bladder cancer [12]. Regarding the MDS, the incidence varies between 2 and 8 % [11,12]. Myelodysplastic syndrome occurs late in the course of the disease (median 60 months after diagnosis) after a median

CP dose of 112 g [11]. It may evolve to an acute leukaemia even after a short time. For most of the patients, the prognosis is bad and the median survival is only 6 to 12 months.

A dose-dependent destruction of germinal tissue by CP leading to temporary or permanent infertility has been shown. The most common findings in men are azoospermia and abnormal serum gonadotropin levels, due to the loss of the germinal epithelium lining the seminiferous tubules and Leydig's cell dysfunction (see also Figure 3a). In women CP-induced ovarian toxicity is heralded by the onset of irregular or infrequent periods and may progress to amenorrhea, permanent infertility and premature ovarian failure with elevated levels of gonadotropins and decreased levels of estradiol leading to physical and emotional consequences. Despite many publications, no data allowing reliable prediction of gonadal toxicity are available. Chapman concluded that by the time 18 g CP has been applied orally, all men will have developed azoospermia. The chance of regeneration decreases with an increasing total dose but an upper limit cannot be given [18]. In women, permanent infertility arises in most of them after total doses greater than 25 g. However, the incidence of ovarian failure depends on age and older women are more likely to progress to premature ovarian failure after therapy because they have a smaller number of oocytes at initiation. In patients with lupus nephritis, CP therapy resulted in ovarian failure in all women older than

30 years, in approximately 50 % of those aged 20 to 30 years and in 13 % of patients younger than 20 years [19]. Recently Manger et al. have described comparable results [20].

### Prevention of Toxicity

The main strategy for reducing CP toxicity is still the reduction of the total dose given to a patient. Stage-adapted treatment in ANCA-associated vasculitis can avoid CP therapy. It has been shown that, in a localized or early systemic manifestation of the disease with normal or only slightly impaired renal function, remission can be achieved using weekly methotrexate (MTX) in an equivalent number of the patients [21]. Remission was delayed among patients with more extensive disease or pulmonary involvement. The longer time to remission may be overcome by higher initial MTX doses and parenteral instead of oral administration of MTX. Regarding patients with renal involvement or with alveolitis or other severe manifestations, oral CP can be replaced safely by intravenous pulse administration, leading not only to a reduction of about 60 % in total dose but also to a marked risk reduction concerning leukopenia and infections [5]. The probability of a toxic event-free period (no death, severe infection, leukopenia or thrombocytopenia) is more than double in patients treated with i.v. pulse CP compared to those receiving daily oral treatment (Figure 2).

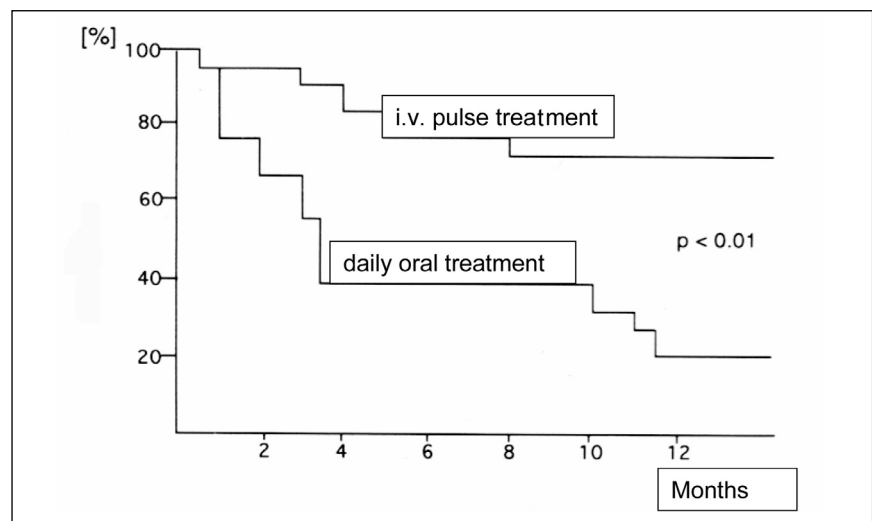


Fig. 2: Probability of a toxic event-free period (no death, severe infection, leukopenia or thrombocytopenia) in patients with ANCA-associated vasculitis receiving daily oral or i.v. pulse administration of CP

Other important issues are the shortening of treatment time and the avoidance of relapses. It could be shown that exposure to CP in patients with systemic, but not life-threatening, ANCA-associated vasculitis with a creatinine of less than 500 µmol/L could be reduced safely by the substitution of azathioprine at remission [6]. Prolonged treatment with drugs with long-term tolerability like azathioprine, mycophenolate mofetil (MMF) or MTX reduces the risk of relapses. However, up to now no data are available regarding the optimal duration of treatment.

In patients with lupus nephritis and a creatinine clearance of more than 30-40ml/min, recent data of randomized studies suggest that MMF given in a daily dose of 2 to 3 g is at least as effective as and safer than CP treatment [22,23]. The results for 72 months' follow-up suggest that i.v. CP pulses followed by MMF, or even azathioprine, are more efficacious and safer than

long-term therapy with i.v. CP (NIH regimen) [24]. However, studies on MMF in lupus nephritis are limited by a small number of patients or a short follow-up. In an ongoing Aspreva Lupus Management Study (ALMS) 358 patients with proliferative lupus nephritis are randomized to receive, in addition to prednisolone, MMF or i.v. CP. If the patients respond to treatment, they are then randomized again after 24 weeks to receive MMF or azathioprine. As recruitment is finished, the first results should be available at the end of the year.

Regarding gonadal toxicity, dose reduction is also an important issue. In our study [25] comparing daily oral to i.v. pulse administration in men, by measuring FSH plasma levels, as well as in Lewis rats, by investigation testis histology and number of foetuses after mating with healthy female rats, pulse administration led to a significantly reduced gonadal toxicity probably due to

the reduction in total dose (Figure 3a, b, 4). Recently, administration of a gonadotropin-releasing hormone analogue in women with severe SLE was associated with a significant reduction in premature ovarian failure [26]. Treatment with an gonadotropin-releasing hormone analogue should be initiated 1 to 2 weeks before the initiation of CP because, during this period, the stimulated gonadal tissue may be rendered more susceptible to the toxic effects [27]. In addition, the potential risk of precipitating a disease flare with hormonal stimulation has to be taken into account in patients with SLE. More information regarding this risk will be available when the results of the prospective randomized study on protection against gonadal toxicity in patients with SLE (PREGO study) have been evaluated [20]. Cryopreservation of fertilised oocytes has been thought to be a possibility for female patients who have already selected a partner. Oocyte cryo-

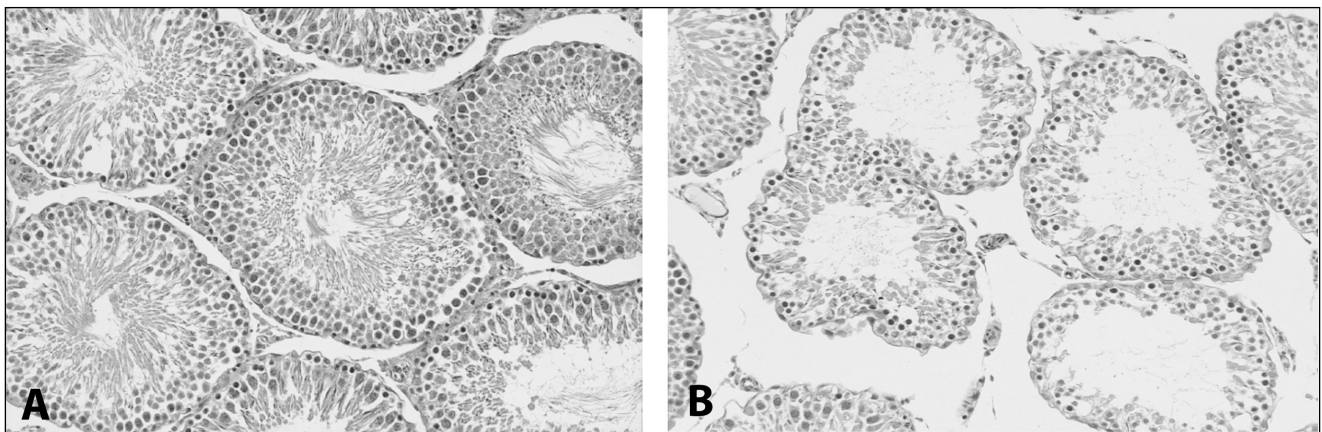


Fig. 3a: Testis histology of a Lewis rat after 6 weeks of pulse CP (A) or daily oral CP (B). A: normal testis histology B: Multifocal hypospermatogenesis of moderate degree

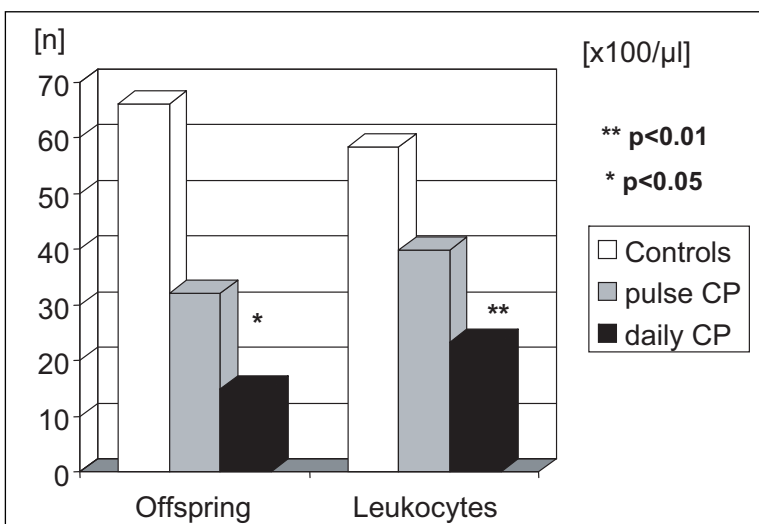


Fig. 3b: Leukocyte counts and number of off-spring of 10 male Lewis rats in each group (pulse or daily oral CP) mated with two female rats

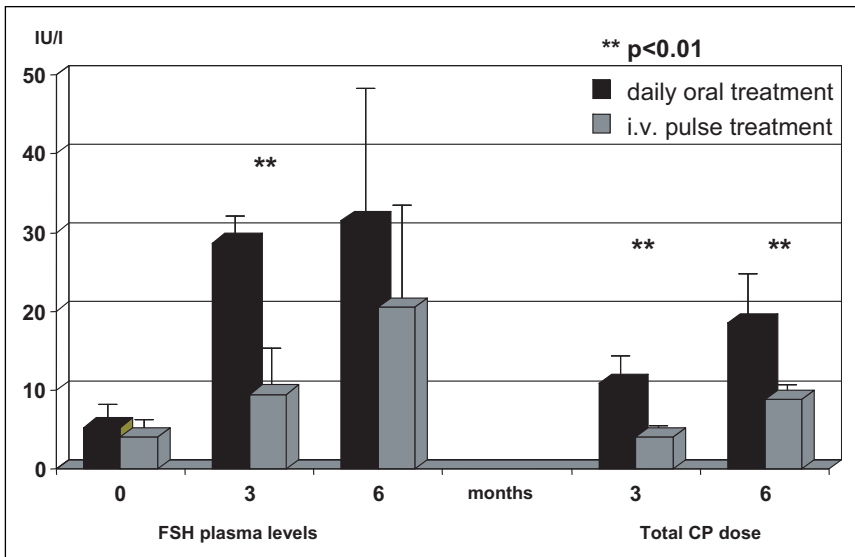


Fig. 4: FSH plasma levels and total cyclophosphamide dose after oral (n=10) and i.v. cyclophosphamide therapy (n=12) in male patients (normal range <7IU/l in men <= 40 and <14 IU/ml in men > 40 years)

preservation remains difficult because the freeze-thaw techniques used appear to inhibit survival and fertilizability. The cryopreservation of ovarian tissue might become a possibility in the future [27].

Preventing testicular dysfunction after CP treatment is still an important issue. The most common strategies include sperm cryopreservation and the use of testosterone to shut down testicular function [28]. Cryostorage of semen has become a standard practice and should be offered routinely to men undergoing gonadotoxic treatment.

The shorter treatment time and a better prevention of relapses together with other non-CP containing treatment regimens and possibly the use of mesna will probably reduce the incidence of bladder cancer in the future. However, up to now there has been no data showing that mesna reduces the risk of a bladder carcinoma. Regarding the early detection, non-glomerular microhaematuria is a risk factor but not always a reliable marker as these episodes were transient and sometimes rare. Cytologic urine examination is of limited usefulness in monitoring patients at risk as it is relatively insensitive for the detection of low-grade bladder cancer [12].

Therefore, in patients with high total CP doses (> 40-50g) a cystoscopy every 1 or 2 years is recommended, even decades after CP administration. Promising results using a proteomic approach identifying marker proteins for

bladder carcinoma in the urine of patients who have not been immune compromised have been published recently [29]. Urinary screening using proteomics may reduce frequency of cystoscopy in the future.

A regular investigation every 6<sup>th</sup> to 12<sup>th</sup> month is necessary for the early detection of skin cancer. For prevention, all patients should reduce their sun exposure and apply a sun blocker, the use of which should be recommended for all immunosuppressive regimens.

To summarize the awareness that is necessary with patients who have been treated with CP, even years ago, I would like to mention the case of a patient of our outpatient unit. A 65-year-old man with primary diagnosis of granulomatous ANCA-associated vasculitis in 1980 had received CP, first orally and later intravenously, with a total dose of more than 100 g. The patient developed end-stage renal disease and received a cadaver kidney transplant in 1991. Function has been excellent up to now with a creatinine below 150 µmol. The immunosuppressive regimen consists of cyclosporin A and prednisolone. In 2000 and 2005 the patient developed relapses involving his upper and lower respiratory tract and eyes together with myalgia, arthralgia and general symptoms. Remission could be achieved with i.v. CP pulses followed by azathioprine. Considering his history of CP treatment and a relapsing course of the disease, what would you suggest for the patient? We recommend urinary exami-

nation for microhaematuria every third month and an annual cystoscopy. We have changed azathioprine to MMF to reduce the risk of skin cancer and recommend a regular skin inspection by a dermatologist every 6<sup>th</sup> month and the rigorous use of sun blocker. A differential blood count should be carried out regularly. However, MDS cannot be avoided and it is not clear if early detection really improves the prognosis.

Finally, it is important to stress that there is hardly another drug with such well known long-term effects. Newer therapeutic regimens gradually replacing CP have proved to reduce toxicity in the short term but there are no data on the long-term effects. We will also have to watch patients carefully following these new treatment regimens.

## References

- Hollander D, Manning RT (1967) The use of alkylating agents in the treatment of Wegener's granulomatosis. *Ann Intern Med* 67: 393-398
- Fauci AS, Haynes BF, Katz P, Wolff SM. (1983) Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 98: 76-85
- Mok CC, Ying KY, Tang S, Leung CY, Lee KW, Ng WL et al. (2004) Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum* 50: 2559-2568
- Mok CC (2004) Cyclophosphamide for severe lupus nephritis: where are we now? *Arthritis Rheum* 50: 3748-3750
- Haubitz M, Schellong S, Gobel U, Schurek HJ, Schaumann D, Koch KM et al. (1998) Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 41: 1835-1844
- Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J et al. (2003) A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349: 36-44
- Davison AMA, Cameron JS, Grunfeld J-P, Ponticelli C, Van Ypersele C, Ritz E et al. (2005) *Oxford Textbook of Clinical Nephrology*. In: Winemans C (Ed.) Vol. 1 (ed Third edition): Oxford University Press
- Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B et al. (1998) A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 9: 444-450
- Ballardie FW, Roberts IS (2002) Controlled prospective trial of prednisolone and cytotoxicity in progressive IgA nephropathy. *J Am Soc Nephrol* 13: 142-148
- Kamar N, Rostaing L, Alric L (2006) Treatment of hepatitis C-virus-related glomerulonephritis. *Kidney Int* 69: 436-439
- Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B et al. (2000) An interdisciplinary approach to the care of patients with Wegener's granulomatosis. *Ann Intern Med* 132: 100-105

- er's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 43: 1021-1032
12. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I et al. (1996) Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 124: 477-484
  13. Reinhold-Keller E, Mohr J, Christophers E, Nordmann K, Gross WL (1992) Mesna side effects which imitate vasculitis. *Clin Investig* 70: 698-704
  14. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J (1998) Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 9: 842-852
  15. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD et al. (1992) Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 116: 488-498
  16. Knight A, Askling J, Ekblom A (2002) Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. *Int J Cancer* 100: 82-85
  17. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA Jr. (1987) Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. *Am J Med* 83: 1-9
  18. Chapman RM (1983) Gonadal injury resulting from chemotherapy. *Am J Ind Med* 4: 149-161
  19. Blumenfeld Z, Shapiro D, Shteinberg M, Avivi I, Nahir M (2000) Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. *Lupus* 9: 401-405
  20. Manger K, Wildt L, Kalden JR, Manger B (2006) Prevention of gonadal toxicity and preservation of gonadal function and fertility in young women with systemic lupus erythematosus treated by cyclophosphamide: the PREGO-Study. *Autoimmun Rev* 5: 269-272
  21. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G et al. (2005) Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 52: 2461-2469
  22. Chan TM, Tse KC, Tang CS, Mok MY, Li FK (2005) Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 16: 1076-1084
  23. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT et al. (2005) Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 353: 2219-2228
  24. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P et al. (2004) Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 350: 971-980
  25. Haubitz M, Ehlerding C, Kamino K, Koch KM, Brunkhorst R (1998) Reduced gonadal toxicity after i.v. cyclophosphamide administration in patients with nonmalignant diseases. *Clin Nephrol* 49: 19-23
  26. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ (2005) Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 52: 2761-2767
  27. Pendse S, Ginsburg E, Singh AK (2004) Strategies for preservation of ovarian and testicular function after immunosuppression. *Am J Kidney Dis* 43: 772-781
  28. Masala A, Faedda R, Alagna S, Satta A, Chiarelli G, Rovasio PP et al. (1997) Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 126: 292-295
  29. Theodorescu D, Wittke S, Ross MM, Walden M, Conaway M, Just I et al. (2006) Discovery and validation of new protein biomarkers for urothelial cancer: a prospective analysis. *Lancet Oncol* 7: 230-240

Prof. Dr. Marion Haubitz  
Department of Nephrology  
Medical School Hannover  
Carl-Neuberg-Str. 1  
30625 Hannover  
haubitz.marion@mh-hannover.de

## Akademie Niere (Hrsg.)

# II. Intensivkurs Nieren- und Hochdruckkrankheiten der Akademie Niere



Der "Intensivkurs Nieren- und Hochdruckkrankheiten" bietet ein Update zu relevanten klinischen Arbeitsfeldern - für Internisten, Chirurgen, Intensivmediziner. Die 43 konzentriert und präzise geschriebenen Beiträge vermitteln umsetzbares Wissen zu den Themen

- glomeruläre Erkrankungen
- Systemerkrankungen
- Elektrolytstörungen, akutes Nierenversagen
- chronische Niereninsuffizienz, Dialyse
- Nierentransplantation
- Hypertonie

Der Band eignet sich als Nachschlagewerk. Er enthält reichhaltige Illustrationen und konkrete Therapieanleitungen.

416 Seiten, ISBN 978-3-89967-391-3, Preis: 40,- Euro

PABST SCIENCE PUBLISHERS

Eichengrund 28, 49525 Lengerich, Tel. ++ 49 (0) 5484-308, Fax ++ 49 (0) 5484-550,  
E-Mail: pabst-publishers.de – Internet: www.pabst-publishers.de