Daily oral versus pulse intravenous cyclophosphamide in the therapy of ANCA-associated vasculitis – preliminary single center experience

Říhová Z.[1], Jančová E.[1], Merta M.[1], Žabka J.[1], Ryšavá R.[1], Bartůňková J.[2], Kolářová I.[2], Tesař V.[1]

[1]First Internal Department of the First Faculty of Medicine, Charles University in Prague

[2]Immunology Department of the Second Faculty of Medicine, Charles University in Prague

Abstract: The aim of the multicentric randomized trial CYCLOPS is to optimize the treatment of induction of remission in patients with generalized, but not immediately life-threatening ANCA (antineutrophil cytoplasmic antibodies) -associated vasculitis. This will be achieved by reducing the dose of cyclophosphamide by administering it as intermittent pulses. The lower cumulative dose will be very probably accompanied with lower toxicity, whereas the effectivity should be comparable. We have enrolled 28 patients to the study. At present, 18 of them are suitable for evaluation. Our preliminary results show that pulse intermittent administration of cyclophosphamide is safer from the point of morbidity and mortality due to infectious complications. In our hands, this treatment modality does not seem to be less effective than the conventional daily oral cyclophosphamide. However, unambiguous results and treatment recommendations will not be available until the final evaluation of all patients enrolled in the trial.

Mailing address: Zuzana Říhová, MD., First Department of Medicine, U Nemocnice 2, 128 08 Praha 2, Czech Republic, Phone +420 224 962 527, E-mail: zrihova@centrum.cz

Introduction

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are systemic autoimmune diseases characterized by pauciimmune necrotizing vasculitis that involves mainly small vessels. They are strongly associated with ANCA (antineutrophil cytoplasmic antibodies). ANCAs are circulating autoantibodies directed against different target antigens of azurophilic granules of polymorhonuclear leucocytes. In WG they are usually directed against proteinase 3 (antiPR3) and have a cytoplasmic type of immunofluorescence (c-ANCA). In MPA the target antigen is myeloperoxidase (MPO) with the perinuclear type of immunofluorescence (p-ANCA). Renal-limited vasculitis (RLV), or idiopathic pauciimmune rapidly progressive glomerulonephritis is an early form that does not involve any other organ but kidney. It is more often antiMPO positive. All these three entities, together with less frequent Churg-Strauss syndrome (CSS), are ranked among ANCA-associated vasculitides. At present, it is unknown whether there is any difference between them in prognosis or response to therapy [1]. Their incidence is not as low as it was originally believed, most probably due to the higher awareness of the disease and the possibility of routine ANCA testing. ANCA-associated vasculitis represents the end-stage renal disease in about 5 % [2].

Untreated, generalized WG and MPA follow a progressive course with a fatal outcome due to vital organ failure. The average survival of untreated patients was 5 months. In the 1970s Fauci and Wolff introduced empirical therapeutic scheme of daily oral cyclophosphamide (CYC) and corticosteroids (prednisolone 1mg/kg/day on a tapered-off basis) for one year after remission achievement. This "Fauci-scheme" dramatically improved the prognosis of the patients. Remission was induced in 80–100 % of cases. However, the toxicity of the regimen caused considerable morbidity and mortality. Moreover, in a long-term follow-up it turned out that at least 50 % of the patients relapse even under continuing immunosuppression or when the therapy is tapered [3]. The aim of the European Vasculitis Study Group (EUVAS) is to improve the clinical, histological and serological diagnostics of vasculitides and to optimize their treatment based on the severity of the disease at presentation. Therefore, EUVAS has designed and conducted several randomized trials and continues to do so. Our center closely cooperates with EUVAS and repeatedly contributes by a substantial number of patients [4].

The aim of the international randomized trial CYCLOPS is to optimize the treatment of induction of remission in patients with generalized, but not immediately life-threatening ANCA-associated vasculitis. There is the intent to reduce the toxicity of induction therapy. This will be achieved by reducing the overall dose of CYC during the induction period by using it in an intermittent pulsed form. There is uniform international consensus that a regimen comprising

pulsed CYC will be associated with less toxicity compared to the current, gold standard, continuous oral CYC regimen. However, there are concerns that lower toxicity may be at the expense of reduced efficacy [5,6]. Consequently, the induction treatment consisted of either continuous oral or pulsed intravenous CYC together with corticosteroids (CS). The maintenance therapy, azathioprine for 12 months, was the same for both limbs. The primary end-point was the rate of remission at 9 months and relapse rate until the 18th month – the disease-free period. Secondary end-points were adverse events of the therapy, cumulative dose of CYC and CS and cumulative damage to the organs affected by vasculitis. Patients with newly diagnosed WG, MPA or RLV with renal involvement without life-threatening manifestation were included into the study. Renal involvement was defined as biopsy proven necrotizing glomerulonephritis and/or microhematuria and proteinuria with serum creatinin 150–500 mmol/L. The inclusion criteria further comprised ANCA positivity and the age limit was 18–80 years. Following patients were a priori excluded: those who had already received immunosupressive treatment, anti-GBM positive, patients with other autoimmune diseases, pregnant women, women without adequate contraception, patients with known malignancy, HbsAg, antiHCV or HIV positive.

Results
The CYCLOPS trial was designed for 160 patients. Between December 1999 and November 2001 our center included a total of 28 patients. Eighteen of them (12 women, 6 men) are to date evaluated. The mean age at presentation was 54.6 years (18–72). Seven patients (5 women, 2 men, mean age 57.9 years) were randomized to the pulse limb (CYC 15 mg/kg body weight in every 2 weeks the 1st month, every 3 weeks until the end of the 6th month). Eleven patients (7 women, 4 men, mean age 52.5 years) were randomized to the oral limb (CYC 2 mg/kg body weight/day month 0–3, 1,5 mg/kg body weight/day month 3–6). The proportion of diagnosis was as follows: in pulse limb: 4×WG, 2×MPA, 1×RLV, in oral limb: 4×WG, 4×MPA, 2×RLV, 1×CSS. All patients had biopsy proven renal involvement and all were ANCA positive. The cumulative dose of CYC in the pulse limb was approximately 150 mg/kg body weight/6 months. In the oral limb the cumulative dose of CYC was more than two-fold, 315 mg/kg body weight/6 months.

  All patients in the pulse limb (100 %) achieved remission, in contrary to only 55 % of patients in the oral limb.

  During the whole period studied, there was only one relapse in the pulse limb that occurred 5 months after the cessation of immunosupressive treatment (i.e. 23 months after the enrollment). The patient was treated again with CYC and CS. After remission achievement she was put on mycophenolate mophetil, which is now gradually tapered.

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The number of infectious complications of immunosupressive treatment was comparable in both limbs (pulse 43 % vs. oral 45 %). However, there were only 14 % of serious events (i.e. those requiring hospitalization) in the pulse limb. One patient had leucopenia ($1,7.10^9$/L) caused by CMV infection and he was successfully treated with ganciclovir. In the oral limb, 27 % of infectious complications were severe and unfortunately resulted in death of the patients. All these three patients died during the induction treatment even though CYC was always stopped as soon as leucopenia and infection were ascertained. The first patient was a 56-year-old woman that died of septic shock despite intensive treatment with antibiotics, antiviral and antimycotic agents. Her leucocytes were constantly above 1.10^9/L. The necropsy revealed pulmonary aspergillosis. The second, 60-year-old patient died despite intensive care including growth factors because of transient leucopenia (nadir leucocytes $0,6.10^9$/l) of respiratory failure due to bilateral pneumonia. She had extensive lung intestitial disease due to WG. The third patient died of febrile neutropenia in another hospital.

The overall mortality was also higher in the oral limb (36 %) compared to the pulse limb (14 %). Apart from three patients from the oral limb that died of infectious complications there was one more death in this group that was not related to the diagnosis or therapy. This patient died in the local hospital due to bleeding caused by cumarine overdose. In the pulse limb, only one death was recorded. This patient died of pulmonary embolism while on maintenance dose of CS (prednisolone 10mg/day). We cannot confidentially exclude that the therapy did not contribute to the fatal complication.

Conclusion
The final results of the multicentric randomized trial CYCLOPS should be published in the second half of 2004 and it will answer the question whether the intermittent pulse application of CYC in the treatment of generalized, but not immediately life-threatening ANCA-associated vasculitides is comparably effective as continuous oral administration. The cumulative dose of CYC in the oral limb of this study is more than two-fold compared to the pulse limb. Therefore, it is practically certain that the toxicity of the pulse regimen will be lower. This benefit might even overweight possibly slightly lower efficacy of the pulse regimen.

Our preliminary results of a small group of patients confirm the higher toxicity of oral CYC that resulted in higher morbidity and mortality in this group. Surprisingly, in our hands, the efficacy of pulse CYC seemed to be better. This was certainly due to the small number of patients and the high mortality in the oral limb. There was no early relapse in the followed-up period (18 months after enrollment). In the pulse limb, one patient relapsed later on.

However, these are only preliminary findings. Unequivocal results and therapeutic guidelines will not be available until the complete evaluation of all patients enrolled to the CYCLOPS trial.

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