TREATMENT OF POLYARTERITIS NODOSA
AND CHURG - STRAUSS SYNDROME.
PROSPECTIVE THERAPEUTIC TRIALS

CHUSPAN

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SUMMARY

OBJECTIVES

1 - MAJOR OBJECTIVES
- Shorten the duration and the adverse effects of immunosuppressive therapy in the most severe forms of polyarteritis nodosa (PAN) or Churg-Strauss syndrome (CSS)
- Avoid immunosuppressive therapy in good prognosis-PAN, but when required, determine the optimal time to prescribe it
- Decrease iatrogenic morbidity in CSS
- Choose the most suited and best tolerated immunosuppressive drug

2 - SECONDARY OBJECTIVES
- Improve the survival rate
- Determine the minimal effective steroid dosage to control the vasculitis and the residual asthma

3 - INCLUSION CRITERIA
- Patients older than 15, with a first episode of PAN or CSS as defined by the American College of Rheumatology

4 - EXCLUSION CRITERIA
- Hepatitis B virus-related PAN
- PAN already under treatment
- Previous history of cancer or hemopathy

5 - PROTOCOL

5 - 1 - Classification
Each patient will be classified at the time of inclusion according to prognostic factors
- Poor initial prognostic factors: patients present at least one of the following factors: nephropathy, gastrointestinal tract involvement (other than isolated abdominal pain), vasculitis-related cardiomyopathy, vasculitis-related central nervous system involvement
- Good initial prognosis: these patients exhibit none of the factors listed above

5 - 2 - Treatments
Patients are enrolled in the protocol and randomized at the onset of corticosteroid therapy whose regimen is the same for both groups.

Corticosteroids
- Methylprednisolone: 15 mg/kg/d intravenously on days 1, 2 and 3 in poor prognosis group and day 1 in the good prognosis group then,
- Prednisone: 1 mg/kg/d for 1 month, followed by progressive withdrawal

Immunosuppressive drugs
- Good prognosis group: immunosuppressive drugs are not initially indicated in this group and are given only if tapering of steroids is not possible beyond 20 mg/d after a period of 4 weeks, if a new specific symptom develops or if a relapse occurs.
  If this need arises, patients are assigned to receive either intravenous pulses of cyclophosphamide (Cy, Endoxan®) (0.6 g/m2/month for 6 months) or oral azathioprine (Az, Imurel®) (2 mg/kg/d during 6 months) as previously randomized at the time of inclusion. The dose are adapted as a function of renal and/or hematologic toxicities.
- Poor prognosis group: each patient is given intravenous Cy (0.6 g/m2 every 4 weeks). These patients will be randomly assigned to receive either 6 or 12 pulses of Cy.
6 - EVALUATION

Results will be analyzed as "intention to treat".
One hundred and eighty-two patients will be enrolled in this study, 110 with poor initial prognoses (55 with 6 pulses, 55 with 12 pulses), and 72 with good initial prognoses (36 with Az, 36 with Cy).
Follow-up is scheduled to last 5 years.

I - INTRODUCTION

Treatment of polyarteritis nodosa (PAN) and Churg-Strauss syndrome (CSS) usually consists of steroids, cytotoxic agents and sometimes, plasma exchanges (1). However these vasculitides are heterogeneous and thus their clinical, immunological or outcome characteristics (2) might necessitate different therapeutic approaches. Although steroids are useful in most cases, no prospective trials have attempted to define which group of patients needs cytotoxic agents, the administration routes and the most effective immunosuppressive agent. Our previous studies (3, 4) have shown that oral cyclophosphamide when given simultaneously with steroids (3), improved the control of the diseases but did not improve their prognoses. In another study (4), we showed that the association of steroids and plasma exchanges, followed by cyclophosphamide in the case of failure, did not improve the prognoses of PAN and CSS. In our most recent protocol (not published) comparing oral and pulse cyclophosphamide, we demonstrated that IV cyclophosphamide was as effective as oral administration and cause fewer side effects. Therefore, we think that, in light of our results on cyclophosphamide morbidity and those reported in the literature (5), other cytotoxic agents should be tested through prospective trials.
We propose here new prospective trials whose objectives are improvement of prognosis concomitantly with reduction of treatment side effects.

PROSPECTIVE THERAPEUTIC TRIALS

Two twin prospective trials, designed to improve the regimens currently prescribed to treat classic (c)-PAN without HBV markers and CSS, are detailed here.

A - PAN WITHOUT HBV MARKERS

A - I - OBJECTIVES

A - I - 1 - Main objectives

A - I - 1 - a - PAN with poor prognostic factors: To shorten the treatment duration for the most severe forms of c-PAN and lowering the treatment side effects.
A - I - 1 - b - PAN with good prognostic factors: To avoid the prescription of cytotoxic agents in patients with good prognostic factors established at the time of diagnosis and to determine the most effective immunosuppressor and the best time for its prescription when such therapy is indicated.

A - I - 2 - Secondary objectives

A - I - 2 - a - Because of the excellent results obtained with the previous trials, improving survival will not be a main objective of the present study but a secondary one. At present the 10-year survival rate of PAN is about of 71 to 72% (3), which is optimal in light of the mean age of the patients (50 years old).
A - I - 2 - b - To determine the minimal dose of steroids able to control the disease in patients are in remission but not cured.

A - II - ENROLLMENT IN THE TRIAL

A - II - 1 - Inclusion criteria

- PAN diagnosed according to the American College Rheumatology (ACR) criteria (6)
- Patients who have not previously been treated with cytotoxic agents and who present the 1st episode of PAN;
- Patients > 15 years old;
- Written informed consent of the patient.

A - II - 2 - Exclusion criteria

- Previously treated PAN or relapses;
- Other vasculitides that do not meet the ACR criteria for PAN;
- PAN related to HBV;
- Microscopic PAN (MPA) defined according to the following criteria (the Chapel Hill nomenclature criteria for the diagnosis of MPA will not be used in this study): - presence of glomerulonephritis and/or lung hemorrhage, absence of microaneurysms, absence of infarcts and vascular nephropathy, absence of HBV infection;
- Previous treatment with cytotoxic agents;
- Cancer or lymphoma,
- Psychiatric disease or patients who probably will not comply with the protocol
- Patients < 15 years old;
A - III - PROTOCOL

A - III - 1 - Initial investigations and stratification

After inclusion, patients will be assigned to 2 groups according to the prognostic factors that have been established through a prospective study (not published).

The group with poor prognostic factors at the time of the treatment assignment comprises patients who present at least one of the following items: 1) vascular nephropathy confirmed by clinical, biological and, if possible, angiographic criteria; 2) gastrointestinal tract involvement except isolated abdominal pain; 3) cardiomyopathy specifically related to PAN; 4) Central nervous system involvement due to PAN (confirmed by brain angiography but not leptomeningeal biopsy).

The group with good prognostic factors includes patients who do not present any of the criteria described above.

To avoid losing track of these patients, should their steroid therapy prove insufficient, at the time of their inclusion they are automatically randomized to receive one of the immunosuppressors regimens (see below), even though the latter may never be prescribed should steroids be curative.

The clinical symptoms and results of investigations will be noted on a form which will include the British Isles Vasculitis Score (BIVAS). The following investigations will be mandatory:

- Biological analyses including inflammatory parameters,
- Immunological tests including the search for antibodies directed against neutrophil cytoplasm (ANCA) and other investigations able to diagnose other vasculitides. Immunofluorescence assays and ELISA will systematically be conducted to identify and titer ANCA.
- Blood samples will systematically be stored before and, if possible, during treatment.
- Biopsies are not mandatory for inclusion in the study. Nevertheless, they are recommended and a copy of the histological reports will be sent to the coordinating center. These results will be collected for further studies on the classification of PAN. In addition to the results, biopsies, angiographies and serum samples will be sent to the coordinating center for analysis by reference centers.

A - III - 2 - Treatments

A - III - 2 - 1 - Steroids

At the beginning of treatment, all patients will receive pulse steroid therapy: 15 mg/kg/d, for 3 consecutive days, followed by Prednisone, 1 mg/kg/d for 3 weeks, the dose will then be tapered by 5 mg every 10 days until half the initial dose is reached. After 3 weeks of this dosage, prednisone will be reduced by 2.5 mg every 10 days until 15 mg/d is reached. After that, the dose will be further tapered by 1 mg every 10 days until the steroids are terminated. In the case of the reappearance or a new increase of ANCA titer, since no data have demonstrated in PAN that the ANCA titer reflects the outcome, the steroid dose will, nevertheless, be decreased according to the schedule described above.

In the group with good prognostic factors, when after 4 weeks, the prednisone dose cannot be reduced, below 20 mg/d or if a relapse occurs, a cytotoxic agent will be added.

As stated above, in the group with good prognostic factors, patients enrolled in the study will be randomized at the time of treatment assignment and not when the randomization effectively occurs.

A - III - 2 - 2 - Immunosuppressors

- Group with good prognostic factors

In this group, immunosuppressors will be given only to patients who relapse, who do not respond to steroid therapy or who need prednisone at a minimal dose of 20 mg/d.

Criteria for relapse, failure and corticodependence are:

- corticodependence and failure: persistence or appearance of clinical and biological manifestations of PAN which do not permit a reduction of prednisone < 20 mg/d. The development of a clinical manifestation will be considered as a relapse. ANCA persistence or reappearance will not be taken into account for diagnosis of a relapse.

- relapse: development of new manifestations of PAN

In these situations, treatment will be determined after randomization between pulse cyclophosphamide and azathioprine.

- Cyclophosphamide will be given at the dose of 0.6 g/m2 on day 4 (i.e., after 3 pulses of methylprednisolone); the second pulse will be administered 2 weeks later, then 2 weeks after the second pulse (depending upon the hemogram). The subsequent pulses will be administered monthly.

In the case of renal insufficiency or in patients over 65 years old, the dose will be 0.5 g/m2 until normal renal function is restored. Six pulses of cyclophosphamide will be administered. Treatment will be prolonged only in the case of failure or relapses. Lymphocyte and neutrophil counts and, if possible CD4 and CD8 counts will be monitored every month. Cotrimoxazole prophylaxis against *Pneumocystis carinii* pneumonia, 1 tablet/day (Bactrim®), will be given when the CD4 is < 300/mm3. Hydration and adjunction of Uromitexan (Mesna®) will be systematic (cf appendix I).

When azathioprine is prescribed, the dose will be 2 mg/kg/day for 6 months. Dose adaptation will follow the same rules as these for cyclophosphamide (cf appendix II).

- Group with poor prognostic factors

Immunosuppression is systematically prescribed at the time of diagnosis and inclusion. Pulse cyclophosphamide will be given at the dose of 0.6 g/m2. The rules for cyclophosphamide administration will be as explained above.

At the time of inclusion, randomization will be made between 6 and 12 pulses.
After completing the assigned cyclophosphamide course, no maintenance therapy has been planned if remission has been obtained. In the case of failure, incomplete remission or relapse under treatment or termination of therapy, other therapeutic modalities will be discussed on a case-by-case basis. The result will be recorded as a treatment failure. New treatment modalities will be discussed with the coordinator.

**A - IV - FOLLOW-UP**

Follow-up examinations will be made on days 15 and 30, then every month for 11 months, then every 3 months for 1 year then, at least, every 6 months for the subsequent years. At each examination, clinical and biological signs will be recorded (including ANCA and blood cell counts).

**A - V - FEASIBILITY**

The French vasculitis network was established in 1981. More than 350 patients have been included in several prospective trials. Twenty to 30 new patients will be included in France and additional inclusions can be made in Europe through the EEC vasculitis network (European Community SYStemic VASculitis trial: ECSYSVAS). In France, the study will be sponsored by the Société Nationale de Médecine Interne and the Société Médicale des Hôpitaux de Paris.

**A - VI - RECRUITMENT AND STATISTICAL ANALYSIS**

(Established with the help of Ph Casassus, Service de Médecine Interne, Hôpital Avicenne, Bobigny and INSERM U 21, Villejuif)

This trial is prospective, randomized and multicentric. The purpose of the study is to determine whether, in patients with poor prognostic factors, the shortest treatment can be as effective as the longest one and associated with fewer side effects. In the group with good prognostic factors, we expect to demonstrate that the less restrictive regimen (azathioprine) will produce fewer side effects and a similar result in terms of survival. In each therapeutic arm the following events will be recorded and subjected to statistical analyses.

**Outcome of PAN**

- Relapse or failure defined by the appearance of new symptoms of the disease or the absence of regression of the initial clinical or biological symptoms or by the development of complications of the disease.
- Death of the patient

**Short - term side effects**

- Number of complications (mainly infectious: viral, bacterial, fungal…)

**Intermediate - term side effects**

- Osteoporosis
- Irreversible amenorrhea (induced menopauses)

**Long - term side effects**

- Cancer or leukemia due to chemotherapy

**Number of patients in the group with poor prognostic factors**

Mortality due to PAN and CSS was roughly 20% at 5 years in our earlier studies (3,4). In our previous trials we demonstrated that: infectious side effects under steroids and pulse cyclophosphamide treatment given for 12 months was 9% (7); when steroids were administered for more than one year, the rate of osteoporotic complications (vertical compression of the vertebrae, fractures…) were 10% (4). Concerning amenorrhea, only data from literature are available and we will take into consideration the results of a study on systemic lupus erythematosus treatment (8) in which it was demonstrated that 15 cyclophosphamide pulses at the dose of 0.5 - 1 g/m2/pulse were responsible for amenorrhea in 39% of the cases and that 6 pulses of cyclophosphamide were responsible of amenorrhea in 16% of the cases. Amenorrhea preceded menopause only in the older women (> 40 years).

From our personal data and those reported in the literature, we have calculated that the cumulated number of events in the group receiving cyclophosphamide during 12 months was 78% (20% deaths, 39% amenorrhea, 9% infectious side effects and 10% fractures attributed to steroids). We hypothesize that 50% of the events will be observed in the group receiving 6 months of cyclophosphamide (20% deaths, 16% amenorrhea, 2% infections, 12% fractures).

Data selected to formulate our hypothesis on cyclophosphamide and azathioprine side effects were derived from our earlier results and from the literature.

For alpha and beta risks of 5%, 55 patients will have to be enrolled in each group; i.e. 110 for the study.

**Number of patients in the group with good prognostic factors**

According to our working hypothesis, the number of events in the group receiving 6 months of cyclophosphamide will be 50%, while the number of events under azathioprine will be 5%. Twelve per cent of osseous side effects attributable to steroids should be added. This hypothesis is speculative because no data are available in the literature on PAN and CSS. The only data available on azathioprine in systemic diseases came from report on Behçet's syndrome (9).

For alpha and beta risks of 5%, 36 patients must be recruited in each group, i.e., 72 for the study.

Inclusion will be pursued for 4 years and follow-up for 5 years. Intermediate analysis will be made 4 years after enrollment of the first patient.

**A - VII - COORDINATION**

B - I - OBJECTIVES

B - I - 1 - Main objectives

B - I - 1 - a - CSS with poor prognostic factors: To shorten the duration of treatment in the most severe forms of CSS and reduce its side effects.

B - I - 1 - b - CSS with good prognostic factors: To avoid prescribing cytotoxic agents for patients with good prognostic factors established at the time of diagnosis and to determine the most effective immunosuppressor and, when indicated, the best time for its prescription.

B - I - 2 - Secondary objectives

B - I - 2 - a - Due to the excellent results obtained in previous trials, improving survival will be a secondary objective of the present study. At present, the 10-year survival rate of PAN and CSS is about 71 to 72% (3), which is optimal in light of the mean age of the groups (50 years old).

B - I - 2 - b - To determine the minimal steroids dose able to control the disease in patients who are in remission but not cured.

B - II - ENROLLMENT IN THE TRIAL

B - II - 1 - Inclusion criteria

- CSS diagnosed according to the ACR criteria (10)
- Patients who have not been received prior treatment with cytotoxic agents and who present the 1st episode of CSS;
- Patients > 15 years old;
- Written informed consent of the patient.

B - II - 2 - Exclusion criteria

- Previously treated CSS or relapses;
- Other vasculitides that do not meet the ACR criteria for CSS;
- Prior treatment with cytotoxic agents;
- Cancer or lymphoma;
- Psychiatric disease or patients who will not comply with the protocol;
- Patients < 15 years old;
- Patients who have not given their informed consent.

B - III - PROTOCOL

B - III - 1 - Initial investigations and stratification

After inclusion, patients will be assigned to 2 groups according to the prognostic factors which have been established prospectively by means of a prospective study (not published).

- The group with poor prognostic factors at the time of the treatment assignment consists of patients who present at least one of the following items: 1) vascular nephropathy confirmed by clinical, biological and, if possible, angio graphic criteria; 2) gastrointestinal tract involvement except isolated abdominal pain; 3) cardiomyopathy specifically related to CSS; 4) central nervous system involvement due to CSS (can be confirmed by brain angiography but not leptomeningeal biopsy).

- The group with good prognostic factors includes patients who do not present any of the criteria explained above.

To avoid losing track of these patients, should their steroid therapy prove insufficient, at the time of their inclusion they are automatically randomized to receive one of the immunosuppressor regimens (see below), even though the latter may never be prescribed should steroids be curative.

- The clinical symptoms and results of investigations will be noted on a form which will include the BIVAS. The following investigations will be mandatory:
  - Biological analyses including inflammatory parameters,
  - Immunological tests including the search for antibodies directed against neutrophil cytoplasm (ANCA) and other investigations able to diagnose other vasculitides. Immunofluorescence assays and ELISAs will be systematically performed to identify and titer ANCA.
  - Blood samples drawn before and, if possible, during treatment will be systematically stored.
  - Biopsies are not mandatory for inclusion in the study. However they are recommended and a copy of the histological report will be sent to the coordinating center. These results will be collected for further studies on the classification of CSS. The biopsies, angiographies and serum samples will be sent to the coordinating center for analysis by reference centers.

B - III - 2 - Treatments

B - III - 2 - 1 - Steroids

At the beginning of treatment all patients will receive pulse steroid therapy:

- Methylprednisolone, 15 mg/kg/d for 3 days in a row, then
- Prednisone, 1 mg/kg/d, for 3 weeks;
- the dose will be tapered by 5 mg every 10 days until half the original dose is reached. After 3 weeks, prednisone will be lowered by 2.5 mg every 10 days until a dose of 15 mg/d is reached. After that, the dose will be further reduced by 1 mg every 10 days until steroids are completely withdrawn. In the case of the reappearance or new increase in the titer of ANCA, because no data have demonstrated in CSS that the ANCA titer reflects outcome, the steroid dose will continue to be decreased according to the protocol.

In the group with good prognostic factors, when the prednisone dose cannot be reduced under 20 mg/day after 4 weeks or if a relapse occurs, a cytotoxic agent will be added. In this group, patients included in the study will be randomized for immunosuppressor therapy at the time of treatment assignment and not when randomization effectively occurs.

B - III - 2 - 2 - Immunosuppressors

- **Group with good prognostic factors**

In this group, immunosuppressors will be given only to patients who relapse, who do not respond to steroid therapy or who need prednisone at a dose > 20 mg/d. Criteria for relapse, failure and corticodpendence are:

- corticodependence and failure: persistance or appearance of clinical and biological manifestations of CSS which do not permit a reduction of prednisone < 20 mg/d. The development of a new clinical manifestation will be considered as a relapse. ANCA persistase or re-occurrence will not be taken into account for diagnosis of a relapse (relapse: development of new manifestations of CSS).

In these situations, treatment will be determined after randomisation between pulse cyclophosphamide and azathioprine.

- Cyclophosphamide will be given at the dose of 0.6 g/m2 on day 4 (i.e., after 3 pulses of methylprednisolone); the second pulse will be administered 2 weeks later, then 2 weeks after the second pulse (depending upon the white blood cell counts). The subsequent pulses will be administered once a month.

In the case of renal insufficiency or in patients > 65 years old, the dose will be 0.5 g/m2 until renal function return to normal. Six pulses of cyclophosphamide will be administered. Treatment will be prolonged only in the case of failure or relapses. Lymphocyte and neutrophil counts and, if possible CD4 and CD8 counts, will be monitored every month. Cotrimoxazole (Bactrim®) prophylaxis against *Pneumocystis carinii* pneumonia, 1 table/d will be given when the CD4 count falls < 300/mm³. Hydration and adjuncion of Uromitexan (Mesna®) will be systematic (cf Appendix).

- Azathioprine will be prescribed at the dose of two 2 mg/kg/d for 6 months. Dose adaptation will follow the same rules as those established for cyclophosphamide (cf Appendix II).

- **Group with poor prognostic factors**

Immunosuppression is systematically prescribed at the time of diagnosis. Pulse cyclophosphamide will be prescribed at the dose of 0.6 g/m². The rules for cyclophosphamide prescription are the same as those given above.

At the time of inclusion, patients will be randomly assigned to receive 6 or 12 pulses.

After completing the cyclophosphamide course, no maintenance therapy has been planned if remission has been obtained. In the case of failure, incomplete remission or relapse under treatment or termination of therapy, other therapeutic modalities will be discussed. The result will be recorded as a treatment failure. New treatment modalities will be discussed with the coordinator.

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- Relapse or failure defined by the development of new symptoms of the disease or the absence of clinical or biological improvement or by the development of complications of the disease.
- Death of the patient.

**Short-term side effects**

- Number of complications (mainly infectious: viral, bacterial, fungal…).
Intermediate - term side effects
- Osteoporosis,
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Long-term side effects
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Number of patients in the group with poor prognostic factors
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From our personal data and those reported in the literature, we calculated that the cumulated number of events in the group receiving cyclophosphamide for 12 months was 78% (20% deaths, 39% amenorrhea, 9% infectious side effects and 10% fractures attributable to steroids). We hypothesize that 50% of the events will be observed in the group receiving 6 months of cyclophosphamide (20% deaths, 16% amenorrhea, 2% infections, 12% fractures).

Data selected to formulate our hypothesis on cyclophosphamide and azathioprine side effects came from the results of our previous studies and from the literature. For a alpha and beta risks of 5%, 55 patients must be enrolled in each group, i.e., 110 for the study.

Number of patients in the group with good prognostic factors
According to our working hypothesis, number of events in the group receiving 6 months of cyclophosphamide will be 50%, while 5% of the events will occur under azathioprine. Twelve per cent steroid-induced bone side effects should be added. This hypothesis is speculative because no data are available in the literature on PAN and CSS. The only information available on azathioprine in systemic diseases is found in a report on Behçet's syndrome (9).

For a alpha and beta risks of 5%, the 36 patients must be recruited in each group, i.e., 72 for the study. Inclusion will be pursued for 4 years and follow-up for 5 years. Intermediate analysis will be made 4 years after the enrollment of the first patient.

B - VII - COORDINATION
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Appendix I : PULSE CYCLOPHOSPHAMIDE
GUIDELINES FOR HYDRATION AND MESNA PRESCRIPTION

Before pulse treatment:
- Urine control by dipsticks looking after proteinuria, leukocyturia and hematuria.
- Hemogram
- Assume a prehydration:
  - oral intake of 1 liter of water at home a few hours before pulse treatment, or
  - infusion of 1000 ml of isotonic glucose or saline serum, 4 hours before the pulse.
- The pulse should be administered as long as possible after a meal in a patient in reclining position. Infusion rate should be slow:
  - immunosuppressor diluted in 500 ml of 5% glucose saline,
  - mean infusion duration: 60 to 120 min.
- MESNA (Uromitexan®) will be administered in order to decrease the bladder toxicity of cyclophosphamide: 60% of the cyclophosphamide dose, i.e., for 1 g pulse, 600 mg administered in several short (20-30 min) infusions
  - at the beginning of the cyclophosphamide pulse,
  - 4 hours and 8 hours after beginning the cyclophosphamide pulse.
- The patient should drink at least 500 ml of water between MESNA infusions. After the pulse, remind to the patient that it is imperative that he/she get up to urinate during night following the pulse.
- Advise women of the risk of amenorrhea and administered the pulses to women taking oral contraception without any wash-out day during the treatment period.
- Hemogram and urine monitoring should be made during the treatment period (see protocol).
- For nurses:
  - Ideally, the cyclophosphamide bolus should be prepared extemporaneously under a laminor flow blood.
  - Avoid inhaling the powder contained in the vial and, in the case of eye or skin contact, ringe abundantly.
Appendix II : CYCLOPHOSPHAMIDE DOSE ADAPTATION

- In patients > 60 years old with impaired renal function, with a creatinine clearance 25 ml/min, the dose of the first pulse of cyclophosphamide will be 0.5 g/m2.
- The same dose reduction schedule will be applied to patients with creatinine clearance 10 ml/min, independently from age.

Dose reduction according to the neutrophil count

Pulse: The neutrophil nadir usually occurs 10 days after infusion. At least two blood cell counts are mandatory for treatment monitoring; 10 days after the pulse and immediately before the next pulse. In patients undergoing dialysis and when the white blood cell count is < 1500/mm3, cell counts will be made twice a week.

The dose will be adapted as a function of the leukocyte count 10 days after the previous pulse.
- When neutrophils are < 1500/mm3: half-the dose will be given
- 1500 < neutrophils < 3000: no dose modification
- neutrophils > 3000: 20% increase the next pulse to a maximum dose of 0.8 g/m2.

Guidelines according to the lymphocyte count

Steroids associated with immunosuppressors are responsible for lymphopenia (mainly CD4). Opportunistic infections, such as Pneumocystis carinii pneumonia have been observed (11). Prophylaxis with Bactrim®, 1 tablet/d, should be given systematically when the CD4 count falls < 300/mm3.

VIII - REFERENCES

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Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis, Clin Exp Rheumatol 1993; 11: 615-621