
Dexamethasone
cyclophosphamide pulse therapy: Some suggestions for modifications

Sir,

It was truly enlightening and educative reading the editorial on dexamethasone pulse therapy in dermatology¹ and the associated viewpoint by Prof. Pasricha² who is widely regarded as the father of pulse therapy in India. Pulse therapy has altered the management and outcome of autoimmune diseases in general and pemphigus in particular. It has slowly but surely replaced the conventional dosing schedules for administration of oral steroids. In response to Dr. Ramam’s query (where do we go from here?), I would like to propose the following suggestions for modifications in the time tested though somewhat rigid protocol of pulse therapy:

1. The total duration of treatment may be individualized according to the severity of the disease and response to therapy. So instead of a regimental approach of a total of 18 months for phases II and III, we may rely on a combination of the clinical severity index, immunofluorescence titers and promptness of response to therapy to decide whether to shorten the duration in quick responders and to extend it in slow responders and smoldering cases.

2. The decision to stop pulse therapy after 18 months in phase II + III can be individualized depending on the results of immunofluorescence (IF) tests. This may decrease the relapse rates. The relapse rate is 13-27% if direct IF (DIF) is negative at the end of treatment but increases to 4-100% if DIF is positive. Similarly, the relapse rate is 24% if indirect IF (IIF) is negative and increases to 57% if IIF is positive at the end of treatment.³,⁴,⁵

3. Serology by IIF can be replaced by ELISA for direct measurement of desmoglein 1 and desmoglein 3 antibodies.

4. As regards the reservations about the toxicity of cyclophosphamide, it is the cumulative dose that increases the chances of malignancies be it carcinoma of the bladder or hematological malignancies.⁶,⁷ A mathematical calculation shows that with a daily dose of cyclophosphamide of 50 mg in phases II and III, the cumulative dose is approximately 25 g. A simple approach to reduce the cumulative dose of cyclophosphamide would be to omit daily administration altogether and replace it with a bolus dose of 500 mg every 4 weeks. The modified phase II would then consist of bolus doses of dexamethasone (100 mg x 3 days) and cyclophosphamide (500 mg on day 2) for 9 months. The modified phase III would consist of only bolus doses of cyclophosphamide 500 mg intravenously every 4 weeks for a further 9 months instead of an oral dose of 50 mg daily. This would reduce the cumulative dose of cyclophosphamide in phases II and III to 9 g only.

5. The bladder toxicity with bolus doses of cyclophosphamide can be further reduced by concomitant administration of MESNA (sodium 2-mercaptopoethane sulfonate) given intravenously. This is easily available in India and is given on the day of administration of bolus cyclophosphamide. The usual dose is equivalent to the dose of cyclophosphamide and is given intravenously over 15-30 minute infusions in 5 divided doses over 24 hrs. It acts by binding to the acrolein metabolite which is implicated in causing hemorrhagic cystitis and the subsequent development of transitional cell carcinoma of the bladder.

6. Regarding the management of patients with fulminant disease in whom activity is not controlled in spite of addition of interval pulses and daily steroids, a different approach may be the use of immunoablative high dose cyclophosphamide without stem cell rescue. This approach has been utilized with success in other autoimmune diseases like systemic lupus erythematosus, acquired aplastic anemia and more recently for paraneoplastic pemphigus.⁸,⁹,¹⁰ It involves use of a high dose of cyclophosphamide
(50 mg/kg) intravenously to induce suppression of a clonal population of B cells followed by administration of granulocyte colony stimulating factor (G-CSF). A high dose of cyclophosphamide spares the progenitor hematopoietic stem cells in the bone marrow which express high levels of aldehyde dehydrogenase, an enzyme causing resistance to cyclophosphamide. However, peripheral lymphoid tissue, being susceptible, is suppressed, with apparent clearing of pre-existing autoimmunity. After a nadir of leucopenia at 8-12 days, there is a repopulation by division of stem cells from the bone marrow which have been spared. G-CSF given during this period hastens this process. Obviously, this approach has to be reserved for severe cases unresponsive to conventional DCP and has to be carried out in institutional settings under cover of broad spectrum antibiotics and anti-candidal drugs. As G-CSF is now available in India (Grastim®) this approach can be tried in selected cases.

7. Persistent oral ulcers are usually treated with topical steroids in a gel/orabase. An alternative approach may be to spray these lesions directly with a steroid inhaler (budesonide or fluocinolone acetonide) used in asthma. Apart from a rapid effect, an additional advantage is that palatal and pharyngeal ulcers that are not accessible to topical steroids can be treated effectively.

I hope that the practicability of these suggestions can be tried in different centers in order to further improve the efficacy of pulse therapy.

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REFERENCES


Response by Dr. Rao and Dr. Laxmi

Sir,

We thank Dr Navin Modi for his comments and for the interest shown in our article. In response to the points raised in his letter, I would like to make the following remarks.

1. Duration of infusion time of cyclophosphamide pulse:

Cyclophosphamide is a pro-drug that is converted by hepatic microsomal enzymes into 4-hydroxy cyclophosphamide. The concentration of 4-hydroxycyclophosphamide is 5 to 10% of the concentration of cyclophosphamide at peak steady state. The half life of 4-hydroxycyclophosphamide is about the same as that of cyclophosphamide ranging between 3-10 hours. Cyclophosphamide is supplied in 50 mg tablets and vials containing powder for injection. Solution for injection is prepared by adding...