Prognostic Factors in Lupus nephritis Treated with Cyclophosphamide Pulses

E.M. Shilova
T.N. Krasnova
A.A. Ivanova
I.E. Tareyeva

Laboratory of Nephrology, and Laboratory of Clinical Morphology, Moscow Medical Academy, Moscow, Russia

Dr. E.M. Shilov, Laboratory of Nephrology, Moscow Medical Academy, Rossolimo str., 11-a, 119021 Moscow (Russia)

Dear Sir,

Intravenous cyclophosphamide (CPA) pulse-therapy is one of the best methods for the lupus nephritis (LN) treatment [1]. Possible severe complications considered that this treatment should be applied only to patients with a high likelihood of success. Thus, prediction of response to therapy obtains considerable significance. The data from renal biopsy, activity (AI) and chronicity (CI) indices, together with certain clinical signs, were found to be prognostic markers in LN patients treated with immunosuppressants [1, 2], but the predictive value of these signs was not supported by other studies [3, 4]. We tried to determine the best predictors among different clinical and morphological variables using a stepwise multiple linear regression analysis of the CPA pulse therapy results.

Thirty-four patients with severe LN (female 32, male 2, nephrotic syndrome in 31, high blood pressure in 23, elevated serum creatinine (Scr) in 15) were treated with CPA pulses (10-20 mg/kg body weight i.v. every 3-4 weeks) combined with high- or middle-dose prednisolone; total CPA dose was 3-20 g. Renal biopsy performed in 21 patients revealed diffuse proliferative LN (DPLN) in 13, focal proliferative LN (FPLN) in 2, membranous gonadotropin (GN) in 3 and sclerosing GN in 3 patients. For further analysis of morphological data biopsies were divided in 3 groups according to the degree of severity: membranous GN 1st degree, DPLN/FPLN 2nd degree, sclerosing GN 3rd degree, and semiquantitative AI and CI [1] were scored. Patients were followed for 3-5 months (mean 15.6). The outcome - the rate of renal functional deterioration - was calculated as:

$$\left(1 - \frac{Scr_0}{Scr_f}\right) / T$$

where $Scr_0$ and $Scr_f$ were the Scr levels before treatment and at the end of the follow-up period, respectively, and $T$ was the duration of follow-up (months).

By the end of the follow-up period positive results were noted in 72% of patients (remission in 19, improvement in 5), negative results in 28% (deterioration in 1, uremia in 4, death in 5). The results were positive in all 3 patients with membranous GN and in 11 patients with DPLN/FPLN; the results were negative in all 3 patients with sclerosing GN and in 4 with DPLN/FPLN. The prognostic value of clinical and morphological signs was evaluated by comparing three statistical models which related the prognostic variables to the outcome with multiple linear regression. The first model included eight clinical variables: sex, age, LN duration, duration of
exacerbation, Scr level, the presence of high blood pressure and he-maturia, and total CPA dose; according to the stepwise multiple regression procedure two of them, LN duration and the Scr level, were chosen as forming the most powerful prognostic clinical model (model 1, table 1), the predictive power of which was 87.6% ($R^2 \times 100\%$). At the second stage one morphological variable (the degree of histological lesions severity) was added to the eight clinical variables. The degree of histological severity and the Scr level were chosen from this set by stepwise regression as the most powerful prognostic model (model 2, table 1); the predictive power of the model increased significantly to 94.7%. The best model including all above-mentioned clinical and morphological variables plus AI and CI was worked out in the third stage: the degree of histological severity and CI were chosen by a stepwise regression procedure (model 3); the predictive power of the model increased significantly to 96.4%

Our study identified the four predictors of the outcome among 11 clinical and morphological variables in LN patients given CPA pulse-therapy: LN duration, Scr level, histological type severity and CI which formed 3 prognostic models. Information yielded by renal biopsy increased the prognostic value of the clinical model significantly; the morphological model (model 3) possessed independent prognostic value. These findings agree in many aspects with those of other authors [1,2] despite different methods of analysis or different outcome criteria.

Practical conclusions can be drawn from these results. (1) Renal biopsy data are most important in predicting effects of CPA pulse-therapy; this is particularly of relevance to patients with long-term nephritis and/or an increased Scr level. (2) Patients with sclerosing type of LN do not respond to CPA pulse therapy. (3) Response to treatment in membranous and DPLN/ FPLN depends on the degree of the sclerotic changes characterized by CI.

References