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Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome

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Abstract

Background. It has been demonstrated that alkylating agents such as cyclophosphamide (CYP) are effective in reducing the risk of relapse in frequently relapsing (FRNS) and steroid-dependent nephrotic syndrome (SDNS). Little is known about prognostic factors in SDNS and FRNS treated by CYP. The objectives of this study are to determine long-term outcomes and factors associated with sustained remission in these patients.

Methods. We retrospectively studied the data from 143 children (104 boys) with SDNS and FRNS treated with CYP in six centres over 15 years. Relapse-free survival was estimated by Kaplan–Meier method. The determinants of long-term remission were assessed by univariate and multivariate analyses using Cox proportional hazard models.

Results. Median age at diagnosis was 3.7 years (interquartile range: IQR 2.3–5.9), and median follow-up was 7.8 years (IQR 4.0–11.8). CYP treatment was introduced after a median time of 1.7 years (IQR 0.7–5.9) after diagnosis. Patients received a median cumulative dose of 168 mg/kg (IQR 157–197) body weight. Relapse-free survival was 65%, 44%, 27% and 13% after 6 months, 1 year, 2 years and 5 years, respectively. In multivariate analysis, sustained remission >2 years was associated with age at treatment >5 years (P = 0.02) and cumulative dose of CYP >170 mg/kg (P = 0.02). Frequently relapsing versus steroid-dependent status and female gender were predictors of borderline significance. Height and body mass index standard deviation score were significantly influenced by CYP treatment.

Conclusion. In our study, long-term efficacy of cyclophosphamide in steroid-responsive nephrotic syndrome is disappointing. Further well-designed trials are required to evaluate the efficacy of other steroid-sparing agents.

Keywords: cyclophosphamide; growth; idiopathic nephrotic syndrome; steroids

Introduction

Idiopathic nephrotic syndrome (NS) is the most frequent glomerular disease in childhood, with reported incidence varying from two to seven cases per 100,000 children [1]. Most patients are steroid responsive, achieving complete remission, but about 70% will relapse [2]. Of those, 60% relapse frequently or become steroid-dependent [2]. In patients with frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS), side effects of steroids can occur, including growth failure, obesity, hypertension, osteoporosis and ocular complications. To reduce the degree of steroid dependency and avoid steroid toxicity, several non-steroid immunosuppressive agents have been proposed to treat these children [3].

Cyclophosphamide (CYP) has been used since the early 1970s in the treatment of NS [4], especially in individuals with marked steroid side effects. CYP has been known to reduce relapse frequency and to induce long-term remission. According to a meta-analysis including 102 children from three trials performed in children with relapsing steroid-sensitive NS, CYP in comparison with prednisone alone results in a significant decreased risk of relapse at 6–12 months (relative risk 0.44, CI 0.26–0.73) [5]. However, the use of daily CYP treatment has been associated with bone marrow depression, increased susceptibility to in-