Hormonal Strategies for Fertility Preservation in Patients Receiving Cyclophosphamide to Treat Glomerulonephritis: A Nonrandomized Trial and Review of the Literature

Alessandro Cigni, MD, Rossana Faedda, MD, Maria Maddalena Atzeni, MD, Piera Veronica Pileri, MD, Sergio Alagna, MD, Pierpaolo Rovasio, MD, Andrea Ercole Satta, MD, Maria Rita Loi, MD, Annalisa Sini, MD, Vincenzo Satta, MD, and Antonio Masala, MD

Background: Prepubertal patients receiving chemotherapy are relatively resistant to cyclophosphamide-induced germinal cell alterations. We studied the possible protective effect of testosterone and triptorelin to inhibit gonadal activity in men and women receiving cyclophosphamide, respectively.

Study Design: Nonrandomized trial.

Setting & Participants: 28 consecutive patients, 11 men and 17 women, from a university medical center with various forms of glomerulonephritis, treated with cyclophosphamide.

Intervention: Men received cyclophosphamide plus testosterone; women were divided into 2 groups: 13 patients (group A) received cyclophosphamide plus triptorelin; 4 (group B) received only cyclophosphamide.

Outcomes & Measurements: Serum follicle-stimulating hormone (FSH) and serum luteinizing hormone levels and, in addition, sperm counts and testosterone levels in men and estradiol levels in women were measured before and after treatment with cyclophosphamide.

Results: All 10 men became azoospermic or severely oligospermic during treatment; after 12 months, all except 1 had a normal sperm count and FSH levels were normal. In women during cyclophosphamide therapy, amenorrhea occurred in all patients. After cessation of therapy, all women in group A started to menstruate regularly, and at the end of follow-up, ovulatory cycles were demonstrated in all women. Hormone levels showed no significant changes throughout the observation period. Six women conceived, and the pregnancies were brought to term successfully without complications. In group B, all 4 women developed sustained amenorrhea; serum FSH and luteinizing hormone levels at the end of therapy and follow-up were significantly higher with respect to baseline; estradiol levels at the end of follow-up were significantly lower compared with baseline and corresponding values in group A.

Limitations: The substudy in men is uncontrolled, the substudy in women is nonrandomized.

Conclusions: The study suggests a protective effect of testosterone and triptorelin against cyclophosphamide-induced gonadal damage in men and women with various forms of kidney disease, respectively.
Am J Kidney Dis 52:887-896.

INDEX WORDS: Cyclophosphamide; glomerulonephritis; testosterone; triptorelin; gonadal damage; fertility; gonadotropin-releasing hormone analogue; chemotherapy; amenorrhea; systemic lupus erythematosus.

Cyclophosphamide is the immunosuppressant drug of choice for the treatment of patients with severe systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody–associated vasculitides, and glomerulonephritis and is widely used for the treatment of patients with various immune-mediated rheumatic, renal, neurological, and hematologic diseases or their complications (reviewed in[1]). However, the impact of this therapy on fertility is an important consideration for many patients.

Several attempts have been made both in animals and humans to preserve gonads from cyclophosphamide-induced damage, with conflicting results (reviewed in[2-5]).

Prepubertal patients who receive large doses of cyclophosphamide seem to recover gonadal function better than adults, suggesting that active germinal cells are more sensitive to cyclophosphamide because of their increased mitotic activity. These observations have led to many trials of suppression of gonadal function, with the aim toward inducing a prepubertal state (reviewed in[4]).

From the Department of Internal Medicine, University of Sassari, Sassari, Italy.

Received December 4, 2007. Accepted in revised form June 18, 2008.

Address correspondence to Alessandro Cigni, MD, Istituto di Patologia Medica, Viale San Pietro n. 8, I-07100 Sassari, Italy. E-mail: cignale@hotmail.com

0272-6386/08/5205-0010$34.00/0
doi:10.1053/j.ajkd.2008.06.017

In a previous pilot study,[6] we showed the protective effect of testosterone administered to men receiving cyclophosphamide for various forms of glomerulonephritis. In the present study, we extend our observations in men and also test the efficacy of a hormonal strategy for fertility preservation in women.

METHODS

In this prospective nonrandomized trial, we enrolled 28 consecutive patients referred to our clinic between 1998 and 2005 (Fig 1), 11 men and 17 premenopausal women (men: age range, 18 to 59 years; average, 32 years; women: age range, 14 to 45 years; average, 30 years) with different immune-mediated diseases (Table 1). Samples obtained by means of percutaneous renal biopsy from all patients were examined by using immune fluorescence, optic, and electron microscopy.

All patients received prednisone and cyclophosphamide as a monthly intravenous bolus according to the protocol reported extensively elsewhere.[7] Briefly, the standardized regimen used for treatment included: methylprednisolone, 250 mg, intravenously for 3 days, followed by prednisone, 1 mg/kg, orally for 2 months, decreased on average by 25 mg every month to a final dosage of 25 mg orally every other day. In addition, all patients received intravenous cyclophosphamide at a dose of 15 to 20 mg/kg of body weight every 30 days for 6 to 9 months. After that, alkylating agent therapy was interrupted and prednisone dosage was tapered according to the steroid-withdrawal schedule.

Average durations of treatment were 7 months for men and 9 months for women. Total cyclophosphamide doses were 6 to 12 g, with an average of 7.7 g, for men and 5.5 to 11 g, with an average of 8 g, for women (Table 1).

Each patient was told of the possible risks of treatment and gave written informed consent. The study protocol was approved by our local ethical committee and is in agreement with the Declaration of Helsinki.

Men

Men received testosterone (a commercial blend of enanthate and propionate esthers of testosterone), 250 mg, intramuscularly every 15 days in addition to prednisone and cyclophosphamide. The increased dose (compared with our previous pilot study[6]) was given to obtain faster inhibition of gonadotropin secretion.[8] Patients began receiving testosterone 30 days before starting cyclophosphamide therapy and

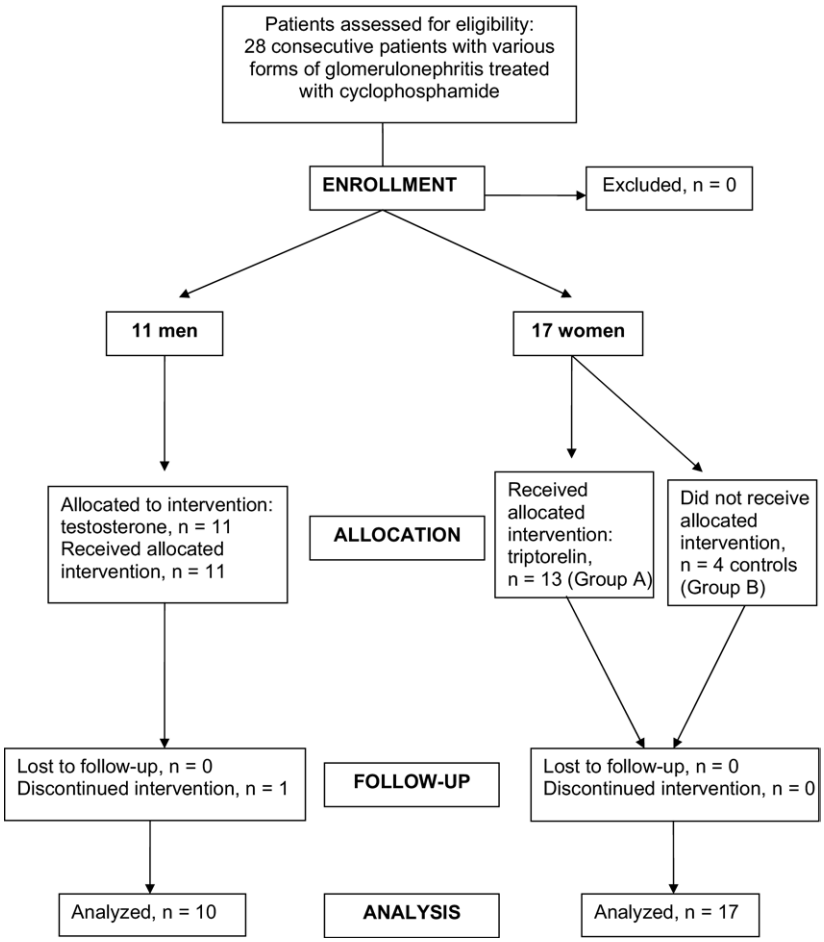

Figure 1. CONSORT flow chart.