Supporting Evidence Document:
Cyclophosphamide Protocol for MCD and FSGS

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Objective

The purpose of this protocol is to facilitate prescribing of cyclophosphamide for the treatment of corticosteroid-dependent, or corticosteroid-resistant minimal change disease (MCD), or focal segmental glomerulosclerosis (FSGS); the following document summarizes the scientific evidence supporting the recommendations.

1. Role of cyclophosphamide

First-line therapy for treating MCD and FSGS is corticosteroids (refer to the BCR corticosteroid protocol), unless the patient is at high risk for corticosteroid-associated toxicity. In patients who have uncontrolled diabetes, a psychiatric condition, severe osteoporosis, morbid obesity, or another reason to not prescribe a corticosteroid, alternative first-line therapy would be calcineurin inhibitors (CNIs) for treating both FSGS and MCD (refer to the BCR CNI protocol). Cyclophosphamide is reserved for patients, who are corticosteroid sensitive, but either corticosteroid-dependent or have frequently relapsing disease. One study found that cyclophosphamide was not effective in patients with corticosteroid-resistant disease, and therefore cyclophosphamide should not be used in this population.[1]

2. Frequently relapsing or corticosteroid-dependent MCD and FSGS

In about 30% of patients, proteinuria will increase while prednisone is being tapered despite previously achieving complete or partial remission.[2] For these corticosteroid-dependent patients, we recommend stopping the taper, temporarily maintaining the current prednisone dose and adding a CNI, or cyclophosphamide.[3] In patients with steroid-dependent MCD, both cyclophosphamide and CNIs induce remission in about 75% of patients.[2,4–8] However, patients treated with cyclophosphamide have a higher likelihood of achieving sustained remission;[9,10] at the expense of being exposed to a more unfavorable side effect profile.

In a prospective trial of 66 children and adults, 11 adults with frequently relapsing or steroid-dependent MCD were randomly assigned to cyclophosphamide (2.5 mg/kg/day for 8 weeks) or cycloSPORINE (5 mg/kg/day for 9 months, then tapered off by month 12).[11] All of the adults achieved remission; 3 patients in each group eventually relapsed, occurring in the first year following therapy with cyclophosphamide, and earlier after discontinuation of cycloSPORINE. Among children, the rate of stable disease at two years was significantly higher with cyclophosphamide (68 vs. 20%). Two other studies confirmed a high relapse rate (about 60%) following cessation of a short cycloSPORINE courses.[9,12]

In a second retrospective study of 14 patients with MCD treated with cyclophosphamide (2 mg/kg/day for 8 weeks), 4 of 5 frequently relapsing patients, and 4 of 9 corticosteroid-dependent patients experienced complete, relapse-free remission.[5] The remaining 5 corticosteroid-dependent patients were able to be weaned off corticosteroids but had subsequent relapses. At final follow-up, 79%

of patients were in complete remission.[5]

In patients with frequently relapsing or corticosteroid-dependent FSGS, data for cyclophosphamide is limited to a few retrospective observational studies.[1,13–22] However, it is fairly established that patients with corticosteroid-resistant FSGS don't respond well to cyclophosphamide.[1] Although cyclophosphamide is considered an option, treatment with a CNI in patients with frequently relapsing or corticosteroid-dependent FSGS may be preferred to avoid toxicity associated with cyclophosphamide.

3. Definition of corticosteroid resistance in a patient with MCD or FSGS

There are conflicting opinions regarding the duration of prednisone therapy that defines corticosteroid-resistance. Some literature suggests the use of alternative immunosuppressive therapy after only 4 to 8 weeks of prednisone, whereas others define resistance as persistent nephrotic syndrome after 4 months of prednisone at a dose of 1 mg/kg/day.[23–26]

The 2012 KDIGO guidelines defines corticosteroid-resistance as persistent nephrotic syndrome after 4 months of prednisone.[3]

4. Short- and long-term cyclophosphamide adverse reactions

Short-term risks while on therapy include leukopenia, infection, and hemorrhage cystitis.[27] Long-term risks include infertility, bladder cancer, solid organ cancers and hematologic cancers. The risk of cancer is associated with cumulative doses over 20 g (there is a 6 fold increase in risk of bladder cancer after 20 to 49 g of exposure, and a 14.5 fold increase in risk after more than 50 g of exposure);[28] as such we have recommended a maximum daily dose of 175 mg which would result in a cumulative cyclophosphamide exposure of 15.75 grams with one cycle.

When diagnosed early, the majority of bladder cancers are superficial. However, there is no high-quality evidence that screening for bladder cancer improves outcomes compared to no screening in high risk populations.[29] In a patient who has received at least one cycle of cyclophosphamide, we recommend screening for bladder cancer annually with urine cytology as long as the patient understands there is uncertainty about the benefits and harms. Based on one systematic review, urine cytology has a sensitivity of 34% and a specificity of up to 99%.[30]

Lower cumulative doses of cyclophosphamide (compared to those associated with cancer) may result in gonadal toxicity in both males and females. A full review of this adverse reaction is available at BCRenalAgency.ca.

5. Cyclophosphamide maximum dose

Controversy exists as to whether to use actual body weight, ideal body weight or to cap the dose when determining the cyclophosphamide dose in obese patients.[31] The American Society of Clinical Oncology recommends using actual body weight when selecting chemotherapy doses regardless of obesity status, as there is no evidence that short-or long-term toxicity is increased among obese patients receiving full weight-based chemotherapy doses.[32] The recommended maximum cyclophosphamide dosage of 175 mg per day found in this protocol is based on opinion to keep cumulative doses under 20 g (*see point 5 on cyclophosphamide adverse reactions*).

6. Cyclophosphamide dosage adjustment

Based on pharmacokinetic studies and data from ANCA vasculitis studies, we recommend a

dosage reduction of cyclophosphamide to avoid bone marrow toxicity in patients over 70 years old, when eGFR is less than 30 ml/min/1.73 m^2 or if the WBC nadir is less than 3.5 x 10^9/L. These recommendations are in line with the KDIGO guidelines[3] but empiric dosage reductions of alkylating agents were not described in any of the original MCD or FSGS studies.

7. Prevention of glucocorticoid-induced osteoporosis, gastrointestinal complications and *Pneumocystic jiroveci* infections

Supporting evidence for prevention of glucocorticoid-induced osteoporosis and gastrointestinal complications has previously been summarized and can be found at BCRenalAgency.ca.

For *Pneumocystic jiroveci* pneumonia (PCP) prophylaxis in immunocomprimised patients without HIV, the American Thoracic Society recommends prophylaxis in patients with inflammatory conditions being treated with immune suppressive therapy and in patients using higher doses of prednisone for over 1 month, especially if concurrently receiving other cytotoxic drugs.[33]

In a recent Cochrane review of 13 randomized or quasi-randomized trials evaluating prophylaxis against PCP in 1,412 immunocomprimised patients (892 adults and 520 children) without HIV infection, trimethoprim-sulfamethoxazole reduced PCP infection [RR 0.15 (95% CI: 0.01-0.62)] with a NNT of 18 to 44 and reduced PCP-related mortality [RR 0.17 (95% CI: 0.03-0.94)] with a NNT of 58 to 926 compared to placebo, no treatment or antibiotics inactive against PCP. There was no significant difference in all-cause mortality or adverse events.[34]

For patients intolerant to trimethoprim-sulfamethoxazole, dapsone, a sulfone antibiotic (distinct from sulfonamide antibiotics) is an option. It is unclear if dapsone displays cross-reactivity in patients with a sulfonamide allergy so it should be avoided in patients who have had a serious reaction such as Stevens-Johnson syndrome.[35] Hemolytic anemia is a dose dependent side effect of dapsone; the risk is low with doses used for PCP prophylaxis unless the patient has a Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.[35] We recommended testing for G6PD prior to starting dapsone and avoiding its use if the patient is found to be deficient.

8. Laboratory

The recommended laboratory measurements monitor known adverse drug reactions caused by cyclophosphamide and is in line with the recommendations made by the KDIGO guidelines.[3] Frequency and type of monitoring can be individualized based on patient tolerability and clinical response.

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