SUPPORTING EVIDENCE DOCUMENT FOR THE BCPRA CYC PROTOCOL FOR MN

BCRenal
an agency of the Provincial Health Services Authority

Objective

The purpose of this protocol is to facilitate prescribing of cyclophosphamide using the modified "Ponticelli regimen" for the treatment of membranous nephropathy; the following document summarizes the scientific evidence supporting the recommendations.

1. Cyclophosphamide versus chlorambucil

Many studies, including the original Ponticelli et al. studies used chlorambucil instead of cyclophosphamide as the alkylating agent in cycle with a corticosteroid.[1—4] This regimen became known as the "Ponticelli regimen."

Subsequent randomized studies found cyclophosphamide to be as good or better than chlorambucil when used in cycle with a corticosteroid.[5,6] However, side effects including leukopenias, anemia, thrombocytopenia, infectious complications and nausea occurred more frequently with chlorambucil.[6] One study by Branten et al. was terminated at their interim analysis due to a particularly high frequency of side effects with chlorambucil compared to cyclophosphamide.[6] One of the Ponticelli et al. studies also reported more severe adverse events leading to discontinuation of therapy with chlorambucil compared to cyclophosphamide (12 vs. 4%).[5] Therefore, we recommend the use of cyclophosphamide instead of chlorambucil.

2. Oral cyclophosphamide versus intravenous cyclophosphamide

Intravenous cyclophosphamide regimens have not been adequately investigated for the treatment of membranous nephropathy and are generally considered to be inferior to oral cyclophosphamide.[7,8]

3. The "Ponticelli regimen"

The modified Ponticelli (cyclophosphamide) regimen consists of a 6-month cyclical regimen of alternating alkylating agents plus intravenous pulse and oral corticosteroids. There are two prospective, open-label, randomized studies, each with 10 years of follow up, investigating the Ponticelli regimen compared to supportive therapy.[4,9] In the first study by Ponticelli et al., they found a higher rate of 10 year dialysis-free survival with treatment, 92% (95% CI: 83 to 100%) vs. 60% (95% CI: 42 to 78%); $p < 0.05$, a higher probability of remission as the first event, 83% (95% CI: 68.6 to 93) vs. 38% (95% CI: 23.4 to 55.4); $p < 0.001$, and better preservation of kidney function.

In the second study by Jha et al. 10-year dialysis free survival with treatment was 89 vs. 65% ($p < 0.05$) and total remission rates were 61 vs. 30%, $p < 0.001$.[9] According to a visual analogue scale, patients who weren't treated with the Ponticelli regimen had lower quality of life scores and more hospital admissions; the authors postulated this to be the result of higher rates of hypertension, edema, hypoalbuminemia and hyperlipidemia requiring more frequent drug therapy.[9]

Reported relapse rates of nephrotic syndrome with the Ponticelli regimen is approximately 25 to 30%, which is lower than with calcineurin inhibitor based treatments (up to 45%).[10] If a relapse occurs, we do not recommend treating with another course of the Ponticelli regimen due to the resulting high cumulative exposure of cyclophosphamide (*see point 5 on cyclophosphamide adverse reactions*).

4. Cyclical cyclophosphamide versus daily cyclophosphamide

Although regimens other than Ponticelli have been studied (such as continuous daily cyclophosphamide and corticosteroid), the long-term safety and efficacy of these regimens are less established and have been given a 2C level of evidence by the KDIGO guidelines compared to 1B for the Ponticelli regimen.[11—14] Not only is the evidence more robust for the Ponticelli regimen but total exposure to cyclophosphamide is reduced by 50% compared to continuous daily dosing.

5. Short- and long-term cyclophosphamide adverse reactions

There is insufficient data to describe the long-term adverse drug reactions associated with the Ponticelli regimen. Short-term risks while on therapy include leukopenia, infection, and hemorrhage cystitis.[15] 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, or 3 additional cancers per 100 patients and a 14.5 fold increase in risk after more than 50 g of exposure, or 7 additional cancers per 100 patients);[16] 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 of the Ponticelli regimen.

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.[17] In a patient who has received at least one cycle of the Ponticelli regimen, we recommend screening for bladder cancer annually with urine cytology as long as the patient understands there is uncertainty about the benefits and harms of this approach. Based on one systematic review, urine cytology has a sensitivity of 34% and a specificity of up to 99%.[18]

6. 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.[19] 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.[20] 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*).

7. 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[10] but empiric dosage reductions of alkylating agents were not described in any of the original membranous nephropathy trials, except for when treatment related leukopenia developed.

8. Evaluating remission status

We recommend assessing for proteinuria remission at the end of the 6-month therapy. Of note, proteinuria can continue to decline for another 6 months or longer after completing the Ponticelli regimen. Therefore, we do not suggest

initiating a new course of immunosuppressants until an observation period of at least 6 months is completed after the end of the modified Ponticelli regimen.

9. 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 in the document titled "Supporting Evidence Document for the Prevention of Glucocorticoid-induced Osteoporosis and Gastrointestinal Complications" at BCRenalAgency.ca.

For Pneumocystic jiroveci pneumonia (PJP) 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.[21] Hence, we recommend it in patients receiving the Ponticelli regimen.

In a recent Cochrane review of 13 randomized or quasi-randomized trials evaluating prophylaxis against PJP in 1412 immunocompromised patients (892 adults and 520 children) without HIV infection, trimethoprim-sulfamethoxazole reduced PJP infection by 85% [RR 0.15 (95% CI: 0.01 to 0.62)] with a NNT of 19 (95% CI: 17 to 42) and reduced PJP-related mortality by 83% [RR 0.17 (95% CI: 0.03 to 0.94)] compared to placebo, no treatment or antibiotics inactive against PJP. There was no significant difference in all-cause mortality or adverse events.[22]

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.[23] Hemolytic anemia is a dose dependent side effect of dapsone; the risk is low with doses used for PJP prophylaxis unless the patient has a Glucose-6- Phosphate Dehydrogenase (G6PD) deficiency.[23] We recommended testing for G6PD prior to starting dapsone and avoiding its use if the patient is found to be deficient.

10. Laboratory

The recommended laboratory measurements monitor known adverse drug reactions caused by the modified Ponticelli regimen and is in line with the recommendations made by the KDIGO guidelines.[10] Frequency and type of monitoring can be individualized based on patient tolerability and clinical response.

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