SUPPORTING EVIDENCE DOCUMENT
CYC INFUSION PROTOCOL FOR GN

BCRenal
an agency of the Provincial Health Services Authority

Objective

The purpose of this pre-printed order is to facilitate prescribing of cyclophosphamide (CYC) and to be used in conjunction with disease-specific protocols that are designed to guide treatment.

1. Laboratory work

The laboratory work ordered on this protocol is to be drawn at the time of infusion for routine monitoring; it is not intended to provide the ongoing laboratory monitoring required when prescribing CYC, this is to be determined by the primary physician and will be addressed in disease-specific treatment protocols.

2. Antiemetics

IV CYC at doses less than or equal to 1500 mg/m^2 is rated as having "moderate emetic risk" or a 30 to 90% frequency of emesis. Therefore, 5-HT3 antagonists are considered the cornerstone for emesis prevention/management.

- The antiemetic regimen found in the CYC infusion protocol is a modified version of the *National Comprehensive Cancer Network Guidelines* for agents with moderate emetic risk.[1]
- Modifications include reducing the duration of 5-HT3 antagonists to 24 hours instead of 48 to 72 hours and removing the concurrent use of dexamethasone as an antiemetic (although it can still be ordered by the physician). This is due to clinical experience that 5-HT3 antagonists as a sole agent on day 1 provides an adequate antiemetic effect.

3. Hydration[2]

The hydration regimen is opinion-based and should be altered depending on the patient's fluid status and urine output.

- MESNA has not been included in this protocol, as according to the BC Cancer Agency CYC Monograph, MENSA is rarely needed when the dose is less than 2 g/m^2.[3] Also, MESNA's short half-life ($t_{1/2}$ = 20 min) suggests it should be continued for at least 24 hours after the discontinuation of CYC, which has a $t_{1/2}$ of 3 to 12 hours.[4] This is not feasible in most outpatient settings.

4. Doses/Frequency:

NIH:

- The "NIH" protocols have been investigated in both SLE and ANCA vasculitis. The monthly dosing is 0.5 to 1 g/m^2 for up to 6 months.
- In a 2004 meta-analysis of studies treating patients with LN class III, IV and V, CYC plus glucocorticoids significantly reduced the risk of doubling of the SrCr (24 versus 40 percent, RR 0.59, 95% CI 0.4-0.88) compared to glucocorticoids alone. This data was from four studies consisting of a total of 228 patients, most of these patients were from NIH trials.[5]
- In ANCA vasculitis, studies have demonstrated that using NIH dosing the addition of CYC to corticosteroids in induction therapy improved the remission rate from 55% to 85%, and decreased the relapse rate three-fold.[6,7]
- The original NIH protocol adjusts dosage based on bone marrow suppression and renal function. The initial dose is 0.75 g/m^2 (0.5 g/m^2 if CrCl less than 30 ml/min); subsequent doses are reduced or increased by 0.25 g/m^2 depending on WBC count at nadir (threshold varies with each study). The dose should not exceed a maximum of 1 g/m^2.
- The BCPRA protocol has set the WBC nadir threshold for reducing dosage at 3.5 x 10^9/L based on studies in ANCA vasculitis. The protocol does not recommend increasing the dose based on bone marrow suppression

but does suggest a relative dose reduction for both renal function and age based on recent experience.

Euro-lupus

- Equivalent efficacy compared to the NIH regimen in the treatment of proliferative LN in Caucasians but it remains uncertain whether its efficacy is equivalent in severe class III/IV LN, and in patients of other ethnicities since neither has been studied.
- No dosage adjustment for renal function or age is recommended, as this was not done in the original study and the dosage is small.

EUVAS

- In a small study, the EUVAS protocol resulted in the same remission rate at 13 months (88%) as oral CYC 2 mg/kg daily for patients with AAV but with less leukopenia HR 0.41 (CI: 0.23 to 0.71).[8]
- However, the EUVAS protocol maybe associated with fewer long-term cancer/ fertility side effects compared to the oral route since the total CYC exposure for a 70 kg person at 3 months is 5.2 grams with EUVAS compared to 12.6 grams with oral 2 mg/kg/day.
- There are no studies comparing the EUVAS protocol vs. the NIH protocol for treatment of ANCA associated vasculitis.
- Dosage adjustments in the BCPRA PPO are based on the original study protocol.[8]

5. Fax to renal pharmacist

The capture of CYC usage in BC GN patients will allow the renal community to track the safety and efficacy of this drug. Currently IV CYC is not being entered into Pharmanet or PROMIS. By informing the designated local renal pharmacist, the CYC dosing will be manually entered into PROMIS.

REFERENCES

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