CYCLOPHOSPHAMIDE

Version 1

SECTION 1

Alternative names

- Cyclophospham
- Endoxana TM
- Cytoxan TM .

Mechanism of Action

Oxazaphosphorine alkylating agent. Cyclophosphamide is a prodrug which undergoes biotransformation primarily by hepatic P450 mixed function oxidases to 4-hydroxycyclophosphamide. This metabolite decomposes spontaneously to produce the bifunctional alkylating species phosphoramide mustard. Bi-functional alkylating agents are thought to exert their cytotoxicity by forming intra-stand and inter-strand DNA cross-links at the N7 position of guanine residues. The generation of phosphoramide mustard is accompanied by the production of the metabolite acrolein which is thought to be partially responsible for the dose-limiting urotoxic effects of the drug. Co-administration of the uroprotectactant agent mesna (Sodium mercaptoethane sulphonate) can help prevent urotoxicity.

Considerations prior to administration

- Concurrent acute urinary-tract infection.
- Urothelial damage following previous cytotoxic chemotherapy or pelvic irradiation.
- Full Blood Count
- Renal function
- Liver function

Adverse effects

Common

- Dose related nausea and vomiting
- Alopecia
- Chemical or haemorrhagic cystitis if administered without mesna or with inadequate hydration and micturition.

Occasional

- SIADH

Rare

Cardiotoxicity presenting as congestive cardiac failure, pericardial effusion and pericardial tamponade. Possible association with previous anthracycline therapy or mediastinal irradiation.

SECTION 2

Recommended routes

Intravenous

Administration

By slow bolus into established IV line or by intravenous infusion over 1 hour.
By IV infusion in Glucose 5%, Sodium chloride 0.9% or Glucose/saline.

Dose/schedule

In order to prevent urothelial toxicity, hydration and mesna are required, particularly with higher daily doses of the drug.

Hydration and mesna

The manufacturers recommend concurrent mesna administration at daily doses of cyclophosphamide in excess of 10 mg/kg. In paediatric clinical practice, mesna is not required until higher daily, or higher cumulative doses per course are exceeded, providing adequate hydration and micturition can be maintained.

> Daily cyclophosphamide doses < 10mg/kg (< 300 mg / m^2)
> No mesna required, maintain fluid intake, encourage frequent micturition.
>
> Daily or total course cyclophosphamide dose 300 mg / m^2 to 1 g / m^2
> No mesna required. Intravenous hydration with glucose/ saline solution at a rate of 3 l / m^2/ 24 hours commencing with the first cyclophosphamide dose and continuing for at least six hours after last cyclophosphamide dose.

Daily or total course cyclophosphamide dose > 1 g / m^2
Intravenous hydration with glucose/saline solution containing mesna at 120% (mg/mg) of the prescribed daily cyclophosphamide dose. Infuse this solution at a rate of 3l / m^2 / 24 hours, commencing 3 hours before the first cyclophosphamide dose and continuing for a minimum of 12 hours after completion of the last cyclophosphamide infusion.

Interactions

Possible with previous or current exposure to hepatic enzyme inducing agents including phenytoin[2].
Concurrent dexamethasone treatment may increase cyclophosphamide metabolism[2]
Concurrent allopurinol administration may decrease cyclophosphamide metabolism[2]

SECTION 3

Dilution specification

Cyclophosphamide is reconstituted with Water for Injections BP to produce a final concentration of 20 mg/ml. At this concentration, absorptive losses onto glass, PVC and polypropylene are thought to be negligible [3,4]
Compatible with glucose 5%, Sodium chloride 0.9% and glucose/saline solutions

Stability

Cyclophosphamide appears to be chemically stable when stored at 4^{o}C. A large body of information exists on stability and compatibility's of cyclophosphamide in solution.[3,4]

Pharmacokinetics

The pharmacokinetics of cyclophosphamide are complex, and since the anti-tumour activity of the oxazaphosphorines rests with their metabolites, little information can be gained from the pharmacokinetics of the parent drug. In children, the plasma half-life of cyclophosphamide ranges from 2.15 to 8.15 hours. Urinary excretion of cyclophosphamide and its metabolites is largely complete within 24 hours of administration [1]. Plasma half-life, apparent volume of distribution and total body clearance increase with increasing dose. Daily administration of cyclophosphamide over 2-4 days results in auto-induction of metabolism but this cannot be demonstrated with repeated 3-weekly courses of the drug [2].

Pharmacodynamics

The role of individual metabolites in producing tumour responses is still not clear. In children, there is significant inter-patient variation in metabolism and pharmacokinetics [1,2], but the clinical consequences of these variations remain unknown. No correlation between either total plasma alkylating activity or individual metabolite plasma AUC's and tumour response has been demonstrated.

References

1. Pharmacokinetics and metabolism of cyclophosphamide in paediatric patients. Tasso, Boddy et al. Cancer Chemother Pharmacol (1992) 30: 207-211
2. Cyclophosphamide metabolism in Children. Yule, Boddy et al. Cancer Research 55, 803-809, 1995
3. The Cytotoxic Handbook. II Edition. Alwood M, Wright P. 1993
4. Handbook of Injectable Drugs. IX Edition. Trissel LA. 1996