

Chemotherapy Protocol

GERM CELL

CISPLATIN-ETOPOSIDE-IFOSFAMIDE

(VIP)

Inpatient Regimen

Regimen

- Germ Cell – InP-Cisplatin-Etoposide-Ifosfamide (VIP)

Indication

- Metastatic Germ Cell Tumours

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity, neutropenia
Ifosfamide	Haemorrhagic cystitis, encephalopathy, nephrotoxicity, neutropenia
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia, neutropenia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es (magnesium, phosphate and calcium) prior to each cycle
- Serum albumin prior to each cycle
- EDTA or calculated creatinine clearance
- Urine dip test for blood every four hours the day of and the day after ifosfamide administration
- Fluid balance monitoring every four hours the day of and the day after ifosfamide administration. Urine output should be maintained above 100ml/hour
- AFP, HCG on day 1 of the cycle

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Prior to each cycle the following criteria should be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

This is a potentially curative regimen. All dose reductions and delays should be discussed with the relevant consultant. In general if these levels are not met then treatment should be delayed for three days at a time. Treatment should re-start as soon as these haematological parameters are met. Dose delays rather than dose reductions are recommended.

Hepatic Impairment

Drug	Bilirubin $\mu\text{mol/L}$		AST/ALT units/L	Dose
Cisplatin	N/A		N/A	No dose modification necessary
Ifosfamide	greater than ULN	or	greater than 2.5xULN	Not recommended
	or ALP greater than 2.5xULN			
Etoposide	26-51	Or	60-180	Consider dose reduction to 50%
	Greater than 51	Or	Greater than 180	Clinical decision

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin*	more than 60	100%
	If the creatinine clearance is 59ml/min or below please discuss with the relevant consultant*	
Ifosfamide	more than 60	100%
	40-59	70%
	less than 40	clinical decision
Etoposide	Greater than 50	100%

	15-50	75%
	Less than 15	50%

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent(s) may then be reduced or discontinued at the discretion of the consultant.

Ifosfamide

In the case of a NCI-CTC grade 1 neurological toxicity, the dose of ifosfamide may be reduced for the next cycle. If a NCI-CTC grade 2 neurological toxicity appears or neurological toxicity worsens despite dose reduction, the ifosfamide should be stopped.

Risk factors for CNS toxicity include a low albumin, renal impairment, prior administration of cisplatin, poor performance status, CNS tumour, bulky pelvic disease, concomitant psychotropic drugs and younger age. Methylene blue 50mg four times a day intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes can be used to prevent or treat ifosfamide induced encephalopathy.

Regimen

21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Etoposide	75mg/m ²	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Cisplatin	20mg/m ²	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 90 minutes
Mesna	120mg/m ²	1,2,3,4,5	Intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
Ifosfamide	1200mg/m ²	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Mesna	600mg/m ²		
Mesna*	600mg/m ²	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes

Dose Information

- Aria is set to dose cap all regimens at 2.4m². This regimen must NOT be capped. Please override any doses that are capped.
- Cisplatin will be dose banded in accordance with the national dose bands (1mg/ml)
- Ifosfamide will be dose banded in accordance with the national dose bands (80mg/ml)
- Mesna will be dose banded in accordance with the national dose bands (100mg/ml NS)
- Etoposide will be dose banded in accordance with the national dose bands (20mg/ml)

Administration Information

Extravasation

- Cisplatin - exfoliant
- Ifosfamide - neutral
- Mesna - neutral
- Etoposide - irritant

Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medication not on Aria are prescribed on the inpatient chart or general electronic prescribing system.

- Antiemetics

Starting prior to chemotherapy

- aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3
 - dexamethasone 4mg once a day on days 1, 2, 3, 4, 5, 6, 7 oral
 - metoclopramide 10mg three times a day when required for nausea oral
 - ondansetron 8mg twice a day on days 1, 2, 3, 4, 5, 6, 7 oral
- Cisplatin pre hydration with 500ml sodium chloride 0.9% with 8mmol magnesium sulphate over 30 minutes. The post hydration is incorporated as part of the ifosfamide and mesna administration. Consider furosemide 40mg oral or intravenous for the treatment of fluid overload.
 - Growth factor support according to local policy, for example;
 - filgrastim or bioequivalent 30 million units once a day for seven days starting on day six of the cycle subcutaneous if less than 80kg, or 48 million units if greater than 80kg.
 - lenograstim or bioequivalent 33.6million units once a day subcutaneous for seven days starting on day 6 of the cycle.
 - pegfilgrastim or bioequivalent 6mg once a day for one day on day six of the cycle.
 - Ciprofloxacin 500mg twice a day for 7 days starting on day 8 of the cycle oral
 - Mouthwashes according to local or national policy on the treatment of mucositis
 - Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.
 - Patients should be encouraged to drink 1-2L of fluids in addition to chemotherapy hydrations. For those unable to do this then a maintenance bag of 100ml/hour should be given when there are no other intravenous fluids running.

References

1. Accord Healthcare Limited. Cisplatin 1mg/ml Concentrate for Solution for infusion summary of product characteristics. Available from: <https://www.medicines.org.uk/emc/product/6111/smpc> [last updated: 16/06/2021].
2. Baxter Healthcare Ltd. Ifosfamide injection1g summary of product characteristics. Available from: <https://www.medicines.org.uk/emc/product/1834/smpc> [last updated 08/02/2022].
3. Medac GmbH. Etoposide 20mg/ml concentrate for solution for infusion summary of product characteristics. Available from: <https://www.medicines.org.uk/emc/product/9070/smpc> [last updated 06/2022].
4. Nichols CR, Catalano PJ, Crawford D et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumours: An Eastern Cooperative Oncology Group, Southwest Oncology Group and Leukemia Group B study. Journal of Clinical Oncology 1998; 16 (4): 1287-1293.

REGIMEN SUMMARY

InP-Cisplatin-Etoposide-Ifosfamide (VIP)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Day 1

1. Warning – Dose Cap in Place

Administration Instructions

ARIA is set to cap all doses in all regimens at $2.4m^2$. This is a potentially curative treatment. Please check the surface area and do not dose cap. Check with the relevant consultant if unsure.

2. Warning – Check supportive medication prescribed

Administration Instructions

1. aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3 oral
2. dexamethasone 4mg once a day on days 1,2,3,4,5,6,7 oral
3. metoclopramide 10mg three times a day when required for the relief of nausea oral
4. ondansetron 8mg twice a day on days 1,2,3,4,5,6,7 oral
5. furosemide 40mg oral or intravenous when required for fluid overload
6. growth factor support according to local policy, for example;
 - filgrastim or bioequivalent 30 million units once a day for seven days starting on day six of the cycle subcutaneous if less than 80kg, filgrastim 48 million units if greater than 80kg.
 - lenograstim or bioequivalent 33.6million units once a day subcutaneous for seven days starting on day 6 of the cycle.
 - pegfilgrastim or bioequivalent 6mg once a day for one day on day six of the cycle
7. ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral

3. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes

4. Etoposide $75mg/m^2$ in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

5. Cisplatin $20mg/m^2$ in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes

6. Mesna $120mg/m^2$ in 100ml sodium chloride 0.9% intravenous infusion over 15 minutes.

7. Ifosfamide $1200mg/m^2$ with mesna $600mg/m^2$ in 1000ml sodium chloride 0.9% over 60 minutes

8. Mesna $600mg/m^2$ in 1000ml sodium chloride 0.9% over 4 hours

Day 2, 3, 4, 5

9. Warning – Check supportive medication prescribed

Administration Instructions

1. aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3 oral
2. dexamethasone 4mg once a day on days 1,2,3,4,5,6,7 oral
3. metoclopramide 10mg three times a day when required for the relief of nausea oral
4. ondansetron 8mg twice a day on days 1,2,3,4,5,6,7 oral
5. furosemide 40mg oral or intravenous when required for fluid overload
6. growth factor support according to local policy, for example;
 - filgrastim or bioequivalent 30 million units once a day for seven days starting on day six of the cycle subcutaneous if less than 80kg, filgrastim 48 million units if greater than 80kg.
 - lenograstim or bioequivalent 33.6million units once a day subcutaneous for seven days starting on day 6 of the cycle.

- pegfilgrastim or bioequivalent 6mg once a day for one day on day six of the cycle
- 7. ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral

10. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
11. Etoposide 75mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes
12. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
13. Mesna 120mg/m² in 100ml sodium chloride 0.9% intravenous infusion over 15 minutes.
14. Ifosfamide 1200mg/m² with mesna 600mg/m² in 1000ml sodium chloride 0.9% over 60 minutes
15. Mesna 600mg/m² in 1000ml sodium chloride 0.9% over 4 hours

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Aug 2022		Alexandra Pritchard Pharmacist	Dr Matthew Wheeler Consultant Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury Hospitals NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.