PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

# IGEV +/- Rituximab Relapsed or Refractory Hodgkin's or Non-Hodgkin's Lymphoma

PROTOCOL REF: MPHAIGEV
(Version No. 1.0)

## Approved for use in:

- Relapsed or refractory Lymphoma (Omit rituximab if CD20 negative)
- ECOG 0-2.
- Patients suitable for a bone marrow transplant (BMT).

## Dosage:

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Rituximab** | **375mg/m$^2$** | IV infusion | Day 1 only (omit if CD20 negative) |
| **Prednisolone** | **100mg** | PO | Days 1 to 4 |
| **Vinorelbine** | **20mg/m$^2$** | IV infusion | Day 2 only *(Day 1 if no rituximab)* |
| **Ifosfamide and Mesna** | **2000mg/m$^2$ & 2000mg/m$^2$** | IV infusion | Days 2 ***to*** 5 *(Day 1 to 4 if no rituximab)* |
| **Mesna** | **400mg/m$^2$** | IV infusion | Four and eight hours post start of ifosfamide infusion on days 2 ***to*** 5 only *(day 1 to 4 if no rituximab)* |
| **Gemcitabine** | **800mg/m$^2$** | IV infusion | Days 2 ***and*** 5 *(Day 1 and 4 if no rituximab)* |

**Maximum of 4 cycles (21 day cycle). NB suitability for a BMT must be made after 2 cycles.**

## Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with rituximab.

- Liaise with BMT team prior to initiation.
- This regimen requires an inpatient stay of at least 5 days
- Ifosfamide can irritate the bladder mucosa. Patients should be encouraged to drink 3L of fluid per 24 hours. Test urine for microscopic haematuria every morning during each cycle as per urine testing protocol (see toxicity management)
- Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects. Ifosfamide neurotoxicity may manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. Recurrence of CNS toxicity after several uneventful treatment courses has been reported. Methylene blue can be used to treat ifosfamide related encephalopathy. Observe for insidious signs of encephalopathy, initially somnolence and confusion (see toxicity management)

## Emetogenic risk:

Severely emetogenic.

## Supportive treatments:

**Rituximab pre-infusion medication:**

- Paracetamol tablet 1gram oral
- Chlorphenamine injection IV bolus 10mg
- Prednisolone 100mg once daily on days 1 to 4 (should be given at least 30 minutes before the rituximab on day 1)

**Supportive medication:**

- Allopurinol PO 300mg once daily for the first cycle
- Aciclovir PO 400mg twice daily
- Aprepitant PO 125mg day 1 and 80mg days 2 and 3
- Chlorhexidine 0.2% mouthwash 10mls four times daily

- Filgrastim S/C 30 or 48 million units once daily on days 7 to 12 (30million units if <70kgs and 48 million units >70kgs) when NOT used for priming. See below for information when used for mobilisation prior to haematopoietic stem cell harvesting
- Metoclopramide PO 10mg three times daily when required
- Ondansetron PO 8mg twice daily when required (IV pre-medication day 2 to 5)
- Anti-seizure prophylaxis should be considered for patients receiving ifosfamide who have a high risk of seizures or CNS disease. Levetiracetam 500-750mg twice daily can be used used and continued until discharge or at clinician discretion. For patients who have had seizures there should be a discussion with the Neurology team. Alternative anti-epileptics can be used on discussion with Neurology. Please consider drug interactions.

## Extravasation risk:

Rituximab – non-vesicant

Vinorelbine – vesicant

Ifosfamide – irritant

Gemcitabine – non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

## Dosing in renal and hepatic impairment:

| | Drug | Creatinine Clearance (mL/min) | Dose adjustment |
|---|---|---|---|
| **Renal** | Ifosfamide | 40 - 59 | 70% dose |
| | | <40 | Clinical decision |
| | | Haemodialysis | Not recommended |
| | Gemcitabine | <30 | Consider dose reduction |
| **Hepatic** | Ifosfamide | Severe impairment | Not recommended due to risk of impaired efficacy |
| | Vinorelbine | Consider dose reduction (66%) in severe liver impairment | |
| | Gemcitabine | Bilirubin >27µmol/L | Consider starting at 80% dose and increase as tolerated. Alternatively start at usual dose and monitor closely. |

## Interactions:

**Rituximab**

No significant interactions

**Vinorelbine**

As CYP 3A4 is particularly involved in the metabolism of vinorelbine, the combination with strong inhibitors of this isoenzyme (for example, ketoconazole, itraconazole, HIV-protease_inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone) can increase the serum concentrations of vinorelbine and the combination with potent inducers of this isoenzyme (for example, rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's wort) can reduce the serum concentrations of vinorelbine.

**Ifosfamide**

The potential for increased formation of metabolites responsible for cytotoxicity and other toxicities (depending on the enzymes induced) must be considered in case of prior or concomitant treatment with, for example:

– Carbamazepine

– Corticosteroids

– Rifampin

– Phenobarbital

– Phenytoin

– St. John's Wort

Inhibitors of CYP 3A4: Reduced activation and metabolism of ifosfamide may alter the effectiveness of ifosfamide treatment. Inhibition of CYP 3A4 can also lead to increased formation of an ifosfamide metabolite associated with CNS and nephrotoxicity. CYP 3A4 inhibitors include: ketoconazole, fluconazole, itraconazole, sorafenib

**Gemcitabine**

Gemcitabine is a radiation sensitizer: be aware if patients are also receiving radiotherapy

For more detailed interactions please refer to the SPC and add a link to the appropriate SPC

## Treatment schedule:

| Day | Time | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|---|
| 1 | 08:30 | **Chlorphenamine** | **10mg** | **IV** | Bolus over 3 to 5 minutes (30 minutes prior to rituximab) |
| | | **Paracetamol** | **1g** | **PO** | 30 minutes prior to rituximab |
| | | **Prednisolone** | **100mg** | **PO** | 30 minutes prior to rituximab |
| | 09:00 | **Rituximab** | **375mg/m$^2$** | **IV** | **CD20+ lymphoma patients only**<br>**≤450mg** 250mL sodium chloride 0.9%<br>**≥500mg** 500mL sodium chloride 0.9%<br>Rate as per rituximab infusion guideline |
| 2 | 08:30 | **Aprepitant** | **125mg** | **PO** | |
| | | **Ondansetron** | **8mg** | **IV** | 100mL sodium chloride 0.9% Over 15 minutes |
| | | **Prednisolone** | **100mg** | **PO** | |
| | 09:00 | **Gemcitabine** | **800mg/m$^2$** | **IV** | 250ml Sodium Chloride 0.9% Over 30 minutes |
| | 09:30 | **Vinorelbine** | **20mg/m$^2$** | **IV** | 50ml Sodium Chloride 0.9% Over 10 minutes |
| | 09:45 | **Ifosfamide & Mesna** | **2000mg/m$^2$ & 2000mg/m$^2$** | **IV** | 1000mL Sodium chloride 0.9% Over 2 hours |
| | 13:45 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 4 hours after ifosfamide and mesna |
| | 14:00 | **Sodium chloride 0.9% 1000mL** | | **IV** | Over 60 mins (hydration post ifosfamide) |
| | 17:45 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 8 hours after ifosfamide and mesna **(Consider oral 1600mg if appropriate)** |
| 3 | 08:30 | **Aprepitant** | **80mg** | **PO** | |
| | | **Ondansetron** | **8mg** | **IV** | 100mL Sodium chloride 0.9% Over 15 minutes |
| | | **Prednisolone** | **100mg** | **PO** | |
| | 09:00 | **Ifosfamide & Mesna** | **2000mg/m$^2$ & 2000mg/m$^2$** | **IV** | 1000mL Sodium chloride 0.9% Over 2 hours |
| | 13:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 4 hours after ifosfamide and mesna |
| | 13:15 | **Sodium chloride 0.9% 1000mL** | | **IV** | Over 60 mins (hydration post ifosfamide) |
| | 17:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 8 hours after ifosfamide and mesna **(Consider oral 1600mg if appropriate)** |
| 4 | 08:30 | **Aprepitant** | **80mg** | **PO** | |
| | | **Prednisolone** | **100mg** | **PO** | |
| | | **Ondansetron** | **8mg** | **IV** | 100mL Sodium chloride 0.9% Over 15 minutes |

| | | | | | |
|---|---|---|---|---|---|
| | 09:00 | **Ifosfamide & Mesna** | **2000mg/m$^2$ & 2000mg/m$^2$** | **IV** | 1000mL Sodium chloride 0.9% Over 2 hours |
| | 13:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 4 hours after ifosfamide and mesna |
| | 13:15 | **Sodium chloride 0.9% 1000mL** | | **IV** | Over 60 mins (hydration post ifosfamide) |
| | 17:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 8 hours after ifosfamide and mesna **(Consider oral 1600mg if appropriate)** |
| 5 | 08:30 | **Ondansetron** | **8mg** | **IV** | 100mL Sodium chloride 0.9% Over 15 minutes |
| | 09:00 | **Ifosfamide & Mesna** | **2000mg/m$^2$ & 2000mg/m$^2$** | **IV** | 1000mL Sodium chloride 0.9% Over 2 hours |
| | 11:00 | **Gemcitabine** | **800mg/m$^2$** | **IV** | 250ml Sodium Chloride 0.9% Over 30 minutes |
| | 13:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 4 hours after ifosfamide and mesna |
| | 13:15 | **Sodium chloride 0.9% 1000mL** | | **IV** | Over 60 mins (hydration post ifosfamide) |
| | 17:00 | **Mesna** | **400mg/m$^2$** | **IV** | 100mL sodium chloride 0.9% over 15 minutes. 8 hours after ifosfamide and mesna **(Consider oral 1600mg if appropriate)** |
| 7 | | **Filgrastim (GCSF)** | **<70kg:** 30 million units **≥70kg:** 48 million units | **SC** | **Non-mobilisation:** Once daily for 6 days **Mobilisation:** Once daily until harvesting complete |

## Haematopoietic Stem Cell Mobilisation:

**The IGEV component of IGEV +/- rituximab should be started on a Thursday to facilitate apheresis starting on a Monday (day 12)**

### Clinical Interventions Prior to Admission

- Arrange for insertion of central venous catheter if insufficient peripheral venous access – apheresis team to assess veins if clinical suspicion that inadequate. Patient may require inpatient admission (ideally ward 4 CCC) if requiring temporary central venous access (femoral vein) and not local to CCC (within 1 hour drive) or if patient is living alone.
- Ensure adequate renal, lung and cardiac function, additional investigations may be required if clinically indicated.
- Discuss with Consultant/HPCT coordinator should any of these results fall out of normal limits
- Book apheresis session in apheresis diary from Day 12.

## Patient Preparation

- Complete appropriate documentation for Stem Cell Therapeutics laboratory to request cryopreservation of HPCs.
- Ensure all blood products are irradiated for a minimum of 7 days pre-harvest.
- Explain procedures of mobilisation chemotherapy and HPC-A collection to patient and discuss potential complications.
- Offer relevant written information available.
- Obtain written informed consent from patient.

## Filgrastim

- Patients should be given the opportunity to be taught how to self-administer filgrastim. A district nurse referral for G-CSF administration should be completes if the patient is unsuitable for self-administration.

## Day(s) of Harvesting – From Day 12

- A peripheral blood CD34 count should be checked.
  - If <5 x$10^6$/L not for apheresis and discus with the transplant team about return following day
  - if 5-10 x$10^6$/L not for apheresis but transplant team to consider plerixafor before returning the following morning
  - if >10 x$10^6$/L for attempt at apheresis.
- One or more harvest procedures may be required to achieve minimal requirement of 2.5 x$10^6$ $CD34^+$/kg, usually target 4–8x$10^6$ $CD34^+$/kg. If results are not within target range clarify with consultant in charge.

## Main toxicities:

| Drug | Toxicity |
|---|---|
| **Ifosfamide** | Bone marrow suppression, nausea and vomiting, haemorrhagic cystitis, ifosfamide induced encephalopathy |
| **Vinorelbine** | Bone marrow suppression, nausea, vomiting, neurotoxicity, constipation, peripheral neuropathy |
| **Gemcitabine** | Bone marrow suppression, nausea, vomiting, fatigue |
| **Rituximab** | Infusion reactions, cytokine release syndrome, hepatitis B reactivation |

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Ongoing |
|---|---|---|---|---|---|
| Clinical Assessment | X | X | X | X | As clinically indicated or at the end of treatment |
| SACT Assessment | X | X | X | X | Every cycle |
| FBC | X | X | X | X | Every cycle |
| U&E & LFTs & Magnesium | X | X | X | X | Every Cycle |
| CrCl (Cockcroft and Gault) | X | X | X | X | Every cycle |
| Virology screen (including Hepatitis B) | X | | | | |
| CT scan** | X | | | | At the end of treatment and if clinically indicated |
| Informed Consent | X | | | | |
| Urine Dip | | X | X | X | Daily while having ifosfamide |
| Neurological assessment | | X | X | X | Daily while having ifosfamide |
| Blood pressure measurement | X | | | | Repeat if clinically indicated |
| PS recorded | X | X | X | X | Every Cycle |
| Toxicities documented | X | X | X | X | Every Cycle |
| Weight recorded | X | X | X | X | Every cycle |
| Blood glucose | X | | | | Repeat if clinically indicated |

## Dose Modifications and Toxicity Management:

## Haematological toxicity:

Proceed on day 1 if-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Platelets ≥ 100 x $10^9$/L |

If neutrophils and platelets below the levels above then discuss with Consultant.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

## Non-Haematological toxicity:

### Ifosfamide Induced Encephalopathy

Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately. Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Refer to Methylthioninium Chloride (Methylene Blue) for Ifosfamide Induced Encephalopathy Clinical Guideline for more information.

### Ifosfamide Induced Haemorrhagic Cystitis

Monitor closely for haematuria following ifosfamide and inform consultant if this occurs.

Managing positive urine dip for blood

| Test result | Action |
|---|---|
| Trace | Re-test |
| + | Re-test. If positive on more than one consecutive test give additional IV bolus mesna. Check fluids and any concurrent mesna is running correctly or oral dose has been taken. |
| ++ / +++ | Double dose of any concurrently running IV mesna. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment |

**Recommended bolus dose:** Mesna intravenous 600mg/m$^2$ or a fixed dose of 1g in 250ml sodium chloride 0.9% over 30 minutes or oral mesna 1800mg. Patients needing bolus mesna should have their infusional mesna or oral doses doubled for all subsequent chemotherapy treatments.

**Infusion Related Reactions:**

| **Non-Haematological toxicities:** | |
|---|---|
| **Rituximab** | |
| Infusion-related Reactions | Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema.<br>Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis.<br>Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion.<br>Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms |

## References:

1. https://www.medicines.org.uk/emc Ifosfamide (accessed 23/2/23)
2. https://www.medicines.org.uk/emc Gemcitabine (accessed 23/2/23)
3. https://www.medicines.org.uk/emc Vinorelbine (accessed 23/2/23)
4. https://www.medicines.org.uk/emc Mesna (accessed 23/2/23)
5. Stefanie D Krens, Gerben Lassche, Frank G A Jansman, Ingrid M E Desar, Nienke A G Lankheet, Prof David M Burger, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. April 2019. The Lancet, [Accessed Feb 2023] Available online at https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30145-7/fulltext
6. BNF available via: https://bnf.nice.org.uk/
7. Küpfer A, Aeschlimann C, Wermuth B, Cerny T. Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. Lancet. 1994 Mar 26;343(8900):763-4.
8. Santoro, A et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007; 92:35-41

## Circulation/Dissemination

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|---|---|
| Date added into Q-Pulse | 23rd June 2023 |
| Date document posted on the Intranet | 23rd June 2023 |

## Version History

| Date | Version | Author name and designation | Summary of main changes |
|---|---|---|---|
| 3/2/23 | 1.0 | **Jennifer Gibson Principal Pharmacist** | New protocol |
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