PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

# Carboplatin and Vincristine

# Pilocytic Astrocytoma

PROTOCOL REF: MPHACVPA
(Version No. 1.0)

## Approved for use in:

Pilocytic Astrocytoma

PS 0-2

## Dosage:

### Induction Phase Cycles 1-3 (21 day cycle)

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | IV | Days 1, 8 and 15 |
| **Carboplatin§** | **AUC* 5** | IV | Day 1 |

### Induction Phase Cycles 4-7 (21 day cycle)

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | IV | Day 1 |
| **Carboplatin** | **AUC* 5** | IV | Day 1 |

### Consolidation Phase: Cycles 8-17 (42 day cycle)

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | IV | Day 1, 8 and 15 |
| **Carboplatin** | **AUC* 5** | IV | Day 1 |

*Use area under the curve (AUC) 5 for GFR calculations utilising Wright formula.

This formula will then need to be used throughout the course of carboplatin treatment. If estimated GFR is used the **Wright formula and AUC 5** must be used for creatinine clearance.

Meditech calculates creatinine clearance using the Wright formula and therefore **creatinine clearance will need to be entered manually to use Cockroft and Gault formula** (applications for calculating creatinine using both formulas are available on the Remote Citrix Web Portal).

**Note that either calculation is an estimate and the dose should be reviewed with the patients clinical condition taken into account**

**Calvert formula for Carboplatin dosage-:**

**Carboplatin dose in mg = AUC x (GFR or CrCl + 25)**

## Emetogenic risk:

Moderately emetogenic.

## Supportive treatments:

Following treatment with carboplatin:

Dexamethasone tablets 4mg orally twice daily for three days

Domperidone 10mg orally three times a day when required

## Extravasation risk:

Carboplatin- Irritant

Vincristine – Vesicant - “dilute and disperse” (warm compress)

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

## Dosing in renal and hepatic impairment:

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|---|---|
| **Renal** | **Carboplatin**<br>Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression. The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function. Carboplatin is contraindicated if GFR or CrCl ≤ 20 ml/min. Do not give carboplatin and discuss with clinical team.<br><br>**Vincristine**<br>No dose adjustments are required |

| | |
|---|---|
| **Hepatic** | **Carboplatin**<br>No need for dose adjustment is required.<br><br>**Vincristine**<br>Bilirubin >51 µmol/L – 50% of original dose |

## Interactions:

Please refer to the SmPC for full list of interactions.

Concomitant use contraindicated

**Yellow fever vaccine**: risk of generalized disease mortal.

Concomitant use not recommended

- **Live attenuated vaccines** (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis).
- **Phenytoin, fosphenytoin**: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- **Ciclosporin** (and by extrapolation **tacrolimus** and **sirolimus**): Excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as **amino glycosides, vancomycin, capreomycin and diuretics**, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance.
- **Loop diuretics (furosemide,indapamide,bumetanide)**: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
- Caution should be exercised in patients concurrently taking drugs known to inhibit/induce drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vincristine sulfate with **itraconazole** or **fluconazole** (known inhibitor of the metabolic pathway) have been reported to cause an earlier onset and/or an increased severity of neuromuscular side-effects, inducers like **St. John's wort** should be given cautiously. This interaction is presumed to be related to inhibition of the metabolism of vincristine.
- When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.
- For a comprehensive list of interactions, please refer to SPC or BNF

## Treatment schedule:

## Induction Phase (Cycles 1-3)

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | Ondansetron | 8mg | PO | 30mins before chemotherapy |
| | Dexamethasone | 8mg | PO | 30mins before chemotherapy |
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |
| | **Carboplatin** | **AUC 5** | **IV** | 500mL glucose 5% over 30 to 60 minutes |
| 8 | Ondansetron | 8mg | PO | 30mins before chemotherapy |

| | | | | |
|---|---|---|---|---|
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |
| 15 | Ondansetron | 8mg | PO | 30mins before chemotherapy |
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |

## Induction Phase (Cycles 4-7)

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | Ondansetron | 8mg | PO | 30mins before chemotherapy |
| | Dexamethasone | 8mg | PO | 30mins before chemotherapy |
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |
| | **Carboplatin** | **AUC 5** | **IV** | 500mL glucose 5% over 30 to 60 minutes |

## Consolidation Phase (Cycles 8-17)

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | Ondansetron | 8mg | PO | 30mins before chemotherapy |
| | Dexamethasone | 8mg | PO | 30mins before chemotherapy |
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |
| | **Carboplatin** | **AUC 5** | **IV** | 500mL glucose 5% over 30 to 60 minutes |
| 8 | Ondansetron | 8mg | PO | 30mins before chemotherapy |
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |
| 15 | Ondansetron | 8mg | PO | 30mins before chemotherapy |

| | | | | |
|---|---|---|---|---|
| | **Vincristine** | **1.5mg/m$^2$ (Max 2mg)** | **IV** | 50mL Sodium Chloride 0.9% over 10 minutes |

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

**For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.**

## Main toxicities:

### Carboplatin

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|---|---|
| **Gastrointestinal** | Nausea, vomiting, diarrhoea, constipation, mucositis |
| **General disorders** | Decreases in serum electrolytes (sodium, magnesium, potassium and calcium)<br>Renal function impairment<br>Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol.<br>Malaise, urticaria. flu-like syndrome, rash, pruritus, alopecia |
| **Haematological** | Neutropenia, anaemia, thrombocytopenia<br>Myelosuppression may be more severe and prolonged in patients with impaired renal function, extensive prior treatment, poor performance status and age above 65. |
| **Hepatobiliary** | Abnormalities of liver function tests (usually mild to moderate).The alkaline phosphatase (ALP) level is increased more frequently than transaminases or total bilirubin. The majority of these abnormalities regress spontaneously during treatment. |
| **Hypersensitivity reactions** | Skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus<br>Risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy |
| **Nervous system** | Paraesthesia and decreased deep tendon reflexes. |
| **Ototoxicity** | Tinnitus and hearing loss |

**Vincristine**

| | |
|---|---|
| **Gastrointestinal** | Constipation, abdominal cramps, paralytic ileus, diarrhoea, nausea, vomiting, oral ulceration |
| **General disorders** | Arthralgia, myalgia |
| **Urology** | Polyuria, dysuria, urinary retention |
| **Vascular disorders** | Hypertension and hypotension have occured |
| **Haematological** | Leukopenia, anaemia, haemolytic anaemia and thrombocytopenia |
| **Nervous system** | Neuropathy |

## Investigations and treatment plan: Induction Phase Cycles 1-3 (21 Day Cycle)

| | Pre | Cycle 1 D1 | Cycle 1 D8 | Cycle 1 D 15 | Cycle 2 D1 | Cycle 2 D8 | Cycle 2 D15 | Cycle 3 D1 | Cycle 3 D8 | Cycle 3 D15 | Ongoing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | | | | | |
| Clinical Assessment | x | x | | | x | | | x | | | As clinically indicated or at the end of treatment |
| SACT Assessment (to include PS and toxicities) | x | x | x | x | x | x | x | x | x | x | Every cycle |
| FBC | x | x | x | x | x | x | x | x | x | x | Every cycle |
| U&E & LFTs & Magnesium | x | x | x | x | x | x | x | x | x | x | Every cycle |
| **Calculate GFR or CrCl and check carboplatin dose using the carboplatin calculator*** | x | x | | | x | | | x | | | Every cycle |
| CT/ MRI scan | x | | | | | | | | | | Every 3 months or if clinically indicated |
| ECG | | | | | | | | | | | If clinically indicated |
| Full observations | x | | | | | | | | | | If clinically indicated |
| Weight recorded | x | x | | | x | | | x | | | Every cycle |
| Height | x | | | | | | | | | | |

* Please refer to:

- 'Dosage' section for full details on carboplatin dosing.

- 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

## Investigations and treatment plan: Induction Phase Cycles 4-7 (21 Day Cycle)

| | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Ongoing |
|---|---|---|---|---|---|
| Clinical Assessment | x | x | x | x | As clinically indicated or at the end of treatment |
| SACT Assessment (to include PS and toxicities) | x | x | x | x | Every cycle |
| FBC | x | x | x | x | Every cycle |
| U&E & LFTs & Magnesium | x | x | x | x | Every cycle |
| **Calculate GFR or CrCl and check carboplatin dose using the carboplatin calculator*** | x | x | x | x | Every cycle |
| CT / MRI scan | | | | | Every 3 months or if clinically indicated |
| ECG | | | | | If clinically indicated |
| Full observations | | | | | If clinically indicated |
| Weight recorded | x | x | x | x | Every cycle |

## Investigations and treatment plan: Consolidation Phase Cycles 8-17 (42 Day Cycle)

| | Cycle 8 D1 | Cycle 8 D8 | Cycle 8 D15 | Ongoing |
|---|---|---|---|---|
| Clinical Assessment | x | | | As clinically indicated or at the end of treatment |
| SACT Assessment (to include PS and toxicities) | x | x | x | Every cycle |
| FBC | x | x | x | Every cycle |
| U&E & LFTs & Magnesium | x | x | x | Every cycle |
| **Calculate GFR or CrCl and check carboplatin dose using the carboplatin calculator*** | x | | | Day 1 of every cycle |
| CT / MRI scan | | | | Every 3 months or if clinically indicated |
| ECG | | | | If clinically indicated |
| Full observations | x | | | Day 1 of every cycle |
| Weight recorded | x | x | x | Every cycle |

## Dose Modifications and Toxicity Management:

## Haematological toxicity:

Proceed on day 1 if-

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

Delay 1 week on day 1 if-

| | |
|---|---|
| Plt ≤ 99 x $10^9$/L | ANC ≤ 0.9 x $10^9$/L |

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. On day 1 of the cycle if blood results do not meet the above levels the patient will miss that dose and be deferred by 1 week. On day 8 and 15 of the cycle if blood results do not meet the above levels the treatment for that day should be omitted and then proceed with the cycle as planned.

## Non- Haematological toxicity:

**Grading and Management of Toxicity**

Toxicity should be grading according to the CTCAEV5 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

| | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| **1st appearance** | Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible | Interrupt treatment until resolved to grade 0/1, then continue at 75 to 80% or AUC 5 of original dose with prophylaxis where possible | Discontinue treatment |
| **2nd appearance** | Interrupt treatment until resolved to grade 0/1, then continue at 75 to 80% of original dose or AUC 5 | Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose or AUC 4 | |

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|---|---|---|---|
| **3rd appearance** | Interrupt treatment until resolved to grade 0/1, then<br>continue at 50% of original dose or AUC 4 | Discontinue treatment | |
| **4th appearance** | Discontinue treatment | | |

## References:

1. SmPC for Carboplatin 10 mg/ml Intravenous Infusion, Hospira – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated June 2020)
2. SmPC for Vincristine 1mg/ml Injection, Hospira – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated April 2022)
3. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

### Circulation/Dissemination

| | |
|---|---|
| Date added into Q-Pulse | 31st May 2022 |
| Date document posted on the Intranet | N/A |

## Version History

| Date | Version | Author name and designation | Summary of main changes |
|---|---|---|---|
| May 2022 | 1.0 | **Hugh O'Neill**<br>**Specialist Oncology Pharmacist** | New Protocol Regimen |
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