Retinoblastoma
PI RET-1 Protocol

NCCN Pacific Working Group Clinical Members

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1.0 AIMS

Primary

To increase the proportion of children with retinoblastoma who are cured.

Secondary

To assess the ability of Pacific Island health systems to deliver chemotherapy according to an adapted protocol.
To assess the ability of Pacific Island health systems to provide supportive care guided by protocol and shared care consultation from New Zealand.

2.0 RATIONALE FOR STUDY DESIGN

Retinoblastoma remains incurable in many regions of the world, with the major obstacles to cure being delayed diagnosis and poor treatment compliance.
The SIOP PODC committee in 2012 generated guidelines for the clinical management
Of retinoblastoma in developing countries and developed a classification system based on the resources available in those settings [1].
This protocol has been developed for use in the Pacific, based on the SIOP PODC guidelines.

Resource Available	**Fiji**	**Tonga**	**Samoa**
Imaging (CT only)	Setting 1	Setting 1	Setting 1
Low- moderate dose chemotherapy	Setting 1-2	Setting 1-2	Setting 1
Radiotherapy*	Not available	Not available	Not available
Ophthalmological treatment	Setting 1	Setting 1	Setting 1
Pathology testing	Not available	Not available	Not available
Genetic testing	Not available	Not available	Not available

*referral to NZ indicated

Retinoblastoma is a highly chemo sensitive tumour that responds well to many low cost chemotherapeutic agents. Regimens that have been used include:

CEV: carboplatin, etoposide, vincristine (currently used in the COG protocols)
CyV: cyclophosphamide, vincristine
CE: carboplatin, etoposide
CyVA: cyclophosphamide, vincristine, actinomycin-D
I(C)E: ifosphamide, etoposide +/- carboplatin

(COG: Children's Oncology Group)
(SIOP: International Paediatric Oncology Society)
(PODC: Paediatric Oncology in Developing Countries)

Fiji:
The chemotherapy protocol should be able to be delivered in its entirety in Fiji.
If ophthalmological assessment or radiotherapy required, referral to Christchurch indicated.

Samoa and Tonga:
Eligible patients in Samoa and Tonga will be referred to Starship (NZ) for surgery and initiation of chemotherapy and then be repatriated for completion of chemotherapy (or palliative care if extra-ocular/metastatic disease)

Staging of Disease:
Several different staging systems have been used, including Reese-Ellsworth (R-E) and the International Classification of Retinoblastoma (ICRB) [3] but the International Retinoblastoma Staging System (IRSS) [2] is easily applicable.

IRSS:
Stage 0 - Patients treated conservatively (subject to presurgical ophthalmologic classifications)

Stage I - Eye enucleated, completely resected histologically

Stage II- Eye enucleated, microscopic residual tumour

Stage III- Regional extension
[(a) overt orbital disease,
(b) preauricular or cervical lymph node extension]

Stage IV- Metastatic disease
[(a) haematogenous metastasis: (1) single lesion, (2) multiple lesions;
(b) CNS extension: (1) prechiasmatic lesion, (2) CNS mass, (3) leptomeningeal and CSF disease].

Risk Stratification:
Low-risk features: isolated choroidal or anterior segment invasion

High-risk features: (these can be present in Stage II eyes)
a) Posterior uveal invasion (includes choroidal invasion) as an independent finding
b) Any degree of concomitant choroid and optic nerve involvement.
c) Tumour involving the optic nerve posterior to the lamina cribrosa as an independent finding.
Other High-risk features: (can be present in Stages II-IV)
d) Scleral invasion
e) Anterior chamber seeding.
f) Ciliary body infiltration
g) Iris infiltration

3.0 PATIENT ELIGIBILITY

Newly diagnosed children with retinoblastoma (unilateral) aged < 18 years are eligible.
Newly diagnosed children with retinoblastoma (bilateral) aged < 18 years **may** be eligible (see 7.0)

4.0 EXCLUSIONS

Children with overt extra ocular disease- these children will be referred for palliative care. (Extra-ocular disease may be difficult to assess when only low resolution CT scans are available)

5.0 INITIAL EVALUATION

5.1 Complete history including family history
5.2 Complete physical examination, including blood pressure
Measure height and weight and calculate surface area
5.3 Chest X-ray
5.4 Full blood and platelet count
5.5 Bone marrow aspirate (BMA)/trephine
5.51 For morphology and cytochemistry
5.6 CSF examination
5.61 For cell count
5.62 For cytospin for malignant cells
5.7 Biochemistry
(liver function/urea, electrolytes, creatinine, urate, calcium, phosphate), calculated renal function, virology (eg. Hepatitis B, varicella) according to clinical circumstances and individual institution's requirements.
5.8 CT/MRI Head and orbits

6.0 REGISTRATION

6.1 Upon diagnosis all patients with Retinoblastoma will be recorded on the unit registry.

7.0 TREATMENT

All eligible patients with **unilateral** retinoblastoma will receive identical therapy-enucleation and 6 cycles of CEV chemotherapy.
Children with **bilateral** disease – discuss with the NZ Paediatric Oncologist
(Fiji with Christchurch and Tonga/Samoa with Starship)
as enucleation of the most affected eye, followed by 6 cycles of CEV chemotherapy may be indicated, provided funding available for review in NZ post chemotherapy, for EUA and local therapy to the remaining eye +/- radiotherapy.

7.1 Option 1:

Up front enucleation then adjuvant (post-operative) CEV chemotherapy x 6 cycles.
(In more than 95% of cases enucleation results in complete removal of tumour with < 5% with microscopically residual disease after enucleation)

7.2 Option 2:

In many countries classified as setting 1, up to ⅔ of children may present with enlarged eyeballs, making enucleation difficult with high risk of rupture, so proceed with neoadjuvant (pre-operative) CEV chemotherapy x 2 cycles, then enucleation, then CEV chemotherapy x 4 cycles post enucleation.
Occasionally surgery may need to be an exenteration- to discuss with the NZ team.)

7.3 CEV chemotherapy

6 cycles (2 days/cycle) given every 28 days.
Each cycle will not commence unless there is count recovery with haemoglobin > 80g/L. absolute neutrophil count >1.0 $x10^9$/L and platelet count >100 $x10^9$/L.
Prehydration and post hydration not required.
Antiemetics: $5HT_3$ antagonist (ondansetron) if available, otherwise metoclopramide for nausea and vomiting.

7.31 Carboplatin 18.6 mg/kg (for children < 36 mths) or 560 mg/m2 (for children ≥ 36 mths)
Administer on Day 1 IV over 1 hour.

7.32 Vincristine 0.05 mg/kg (for children < 36 mths) or 1.5 mg/m2 (for children ≥ 36 mths)
Maximum dose 2mg.
Administer on Day 1 by IV push over 1 minute (or) by infusion via minibag as per institutional policy

7.33 Etoposide 5 mg/kg (for children < 36 mths) or 150 mg/m2 (for children ≥ 36 mths)
Administer on Days 1 and 2, IV over 1 hour.

8.0 COMPLETION OF THERAPY

Following completion of therapy the patient moves into follow-up.
It is unlikely that regular eye surveillance will be available in Setting 1 countries.

8.1 Patients will need to be followed at set intervals (ideally 6 weekly for 6 months then 3 monthly for 2 years then 6 monthly for 2 years then annually) to document progress including continuing remission and late effects of treatment (if any- expected to be minimal). A full blood count should be performed at the first visit off treatment and if normal no further blood tests indicated.

8.2 When off treatment 6 months, provided well and in remission, re-immunise as per recommended schedule- refer guideline on infections.

8.3 Relapse/recurrence including development of extraocular disease- for palliative care

9.0 PARENT INFORMATION SHEET

Your child has been diagnosed with a Retinoblastoma (Childhood cancer of the eye arising in the retina). The affected eye will need to be removed in an operation called enucleation, and examined under the microscope. To prevent the spread of disease beyond the eye in the future your child will need to have chemotherapy, either before (for very large tumours) or after enucleation to hopefully prevent the cancer from coming back. Retinoblastoma is now a curable disease in some children, provided it has not spread beyond the eye.
The chemotherapy is given for six months.

The chemotherapy drugs are called **carboplatin** and **vincristine** on Day 1 of the treatment, and **etoposide** on Days 1 and 2 of treatment.

Your child will have to stay in the clinic for about 6 hours on Day 1 and 2 hours on Day 2.
All 3 drugs (carboplatin, etoposide and vincristine) will be given by inserting a needle under the skin into a vein in your arm.

- The carboplatin and etoposide will be given slowly for 1 hour.
- The vincristine will only take a few minutes to give.
- Your child will not have chemotherapy on days 3 – 27 (this is called a rest period). One cycle of treatment lasts 27 days.
- A new cycle will start on the 28th day of the last cycle. Your child will repeat the chemotherapy for a total of 6 times, which will last 6 months.

MEDICAL TESTS

Your child will need to have the following scans, tests or procedures.

- Physical examination
- Medical History
- Blood tests
- Bone marrow aspirate and trephine
- Lumbar puncture for collection sample CSF
- Chest Xray
- CT or MRI scan (to see if any cancer can be found outside the eye)

SIDE EFFECTS/ RISKS

There is a risk of bruising and a small risk of infection at the site where the blood is drawn.
Your child may have side effects which may be mild or very serious Your consultant will discuss in detail the treatment protocol your child will receive, including the side effects and possible complications associated with treatment. You need to be informed of the range of possible side effects. Some children will experience few of the side effects while other children may experience many. Many side effects go away soon after the patient stops taking the chemotherapy drugs.

Risks and side effects related to <u>carboplatin</u> include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• fewer red blood cells and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make your child feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes your child to bruise and bleed more easily
• Abnormal levels of certain salts in the body like sodium and potassium
	• Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure)
	• Rash
	• Metallic taste
	• Numbness and tingling in the fingers and toes
	• Hair loss
	• Constipation or diarrhoea
	• Pain in your child's abdomen
	• Temporary changes in vision
	• Damage to the ear causing hearing and balance problems
	• A feeling of weakness and/or tiredness
	• Inflammation and/or sores in the mouth (and/or throat and /or oesophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)
		• Damage to the liver
		• Damage to the kidney
		• Leukaemia later in life

Risks and side effects related to <u>etoposide</u> include those which are:

Likely	Less Likely	Rare but serious

• Nausea and vomiting
• Hair Loss
• A feeling of weakness or tiredness
• Fewer red and white blood cells and platelets in the blood
  ○ a low number of red blood cells can make your child feel tired and weak
  ○ a low number of white blood cells can make it easier to get infections
  ○ a low number of platelets causes your child to bruise and bleed more easily
	• Loss of appetite
	• Decreased blood pressure during the infusion which may require treatment
	• Rashes
	• Diarrhoea
	• Pain in the abdomen
	• Mouth sores
	• Tingling sensation or loss of sensation in fingers or toes
	• A feeling of extreme tiredness or weakness
	• The finger or toe nails may loosen from their nail beds
	• Inflammation of the vein through which the medication was given
	• Chest pain
		• Damage to the liver
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• A new cancer or leukaemia resulting from this treatment
		• Severe rashes which can result in loss of skin and damage to mucous membranes
		• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Damage to the heart muscle which may make your child feel tired, weak, feel short of breath, and retain fluid

Risks and side effects related to <u>vincristine</u> include those which are:

Likely	Less Likely	Rare but serious
• Hair loss • Reversible nerve problem that may affect the way your child walks or the feelings in your child fingers or toes • Constipation	• Jaw pain • Headache • Muscle Weakness • Pain and bloating in your child's abdomen (gut) • Numbness and tingling • Wrist or foot drop • Drooping eyelids • Double vision, difficulty seeing at night • Hoarseness of your child's voice • Difficulty sweating • Abnormal walk with foot slapping • Difficulty with urination or increase desire to urinate • Dizziness and low blood pressure when you stand • Abnormal hormone function which may lower the level of salt in the blood • A mild drop in white blood cells, red blood	• Complete stoppage of your child 's intestinal activity which can result in intestinal blockage • If the drug leaks out of the vein when being administered it will cause damage to nearby tissue • Seizures • Vocal cord paralysis • Difficulty breathing • Inability to walk • Decreased ability to hear clearly • Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness • In combination with other chemotherapy drugs: damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which

	cells and platelets in the blood o a low number of red blood cells can make your child feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets causes your child to bruise and bleed more easily	makes it look larger

We hope this information is helpful to you and will enable you, your child and family to understand and cope with the necessary treatment which we hope will achieve cure

10.00 TREATMENT SCHEMA

DEMOGRAPHICS				
Name:				**Summary #1, Date:**
				Hospital:
NHI: **Gender:** **DOB:**				NZ Paediatric Oncologist
DIAGNOSIS: STAGE and RISK STRATIFICATION				
RETINOBLASTOMA:				Date Diagnosis:
	•	DIAGNOSIS: **UNLATERAL RETINOBLASTOMA**		
	•	INITIAL LOCATION:		
	•	**INITIAL TREATMENT: Enucleation**	**Date of surgery:**	
	•	Histology		
	•	Bone Marrow		
	•	Imaging		
	•	STAGE		
	•	RISK		
OTHER DIAGNOSES: Nil				
TREATMENT PLAN				
RELAPSE TREATMENT PLAN : COG ARET0332				**Date Start:**
	•	INDUCTION: CEV x 6		
	•	Local Therapy:		

Date		**Course**	Weight …….kg Height…….. cm	
		Pretreatment	CT/MRI scan, CXR, FBC, renal function, LFT, audiology (if available)	
	CEV	1	**Vincristine** 0.05 mg/kg if <36 months (or 1.5mg/m2 if ≥36months) IV push on day 1 **Carboplatin** 18.5mg/kg if <36months (or 560mg/m2 if ≥36months) IV over 60 minutes on day 1 **Etoposide** 5mg/kg if <36months (or 150mg/m2 if ≥36months) over 60 minutes on day 1 and day 2 NOTE: decimal place for dosing, DOUBLE CHECK. Give each cycle with 28 day interval , provided count recovery with Hb >80g/L, ANC >1.0 x10^9/L, Platelets >100x10^9/L NOTE: order of administration: Vincristine, followed by carboplatin then etoposide	
	CEV	2	Carboplatin, etoposide, vincristine: SEE NOTES ABOVE	
	CEV	3	Carboplatin, etoposide, vincristine: SEE NOTES ABOVE	
	CEV	4	Carboplatin, etoposide, vincristine: SEE NOTES ABOVE	
	CEV	5	Carboplatin, etoposide, vincristine: SEE NOTES ABOVE	
	CEV	6	Carboplatin, etoposide, vincristine: SEE NOTES ABOVE	

SUPPORTIVE CARE	
Antiemetics: $5HT_3$ antagonist (ondansetron) if available, otherwise metoclopramide.	Immunisations: **Fertility:** N/A
Febrile Neutropenia: As per local country protocol. Avoid aminoglycosides as Carboplatin is also nephrotoxic	**Hearing:** Audiology ideally prior to chemotherapy and at end of treatment
Blood Products: Standard blood products. Transfuse red cells if Hb < 80g/L Transfuse platelets if Platelets <20 x 10^9/L	**RENAL: Creatinine and estimated GFR** **PCP prophylaxis: Cotrimoxazole at weekends**
Nutritional Support: to be assessed, may require nasogastric support	**Fungal prophylaxis**: fluconazole as indicated

APPENDIX:

1) *Pneumocystis* prophylaxis

All patients should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) throughout therapy.

The dose is 5 mg/kg/day of TMP given in two divided doses (bd) for 2 days/week (usually Saturday and Sunday).

2) Carboplatin therapy

i) Prehydration and post hydration not required unless:
the consultant directs that concomitant **hydration** may be added.
For children less than 12kg or infants, pre and post hydration may be required, to discuss with a consultant.

ii) $5HT_3$ antagonist (ondansetron) if available, otherwise metoclopramide for nausea and vomiting.

iii) Give carboplatin in 50ml or 100mls 5% glucose over 1 hour

iv) If a patient has had a hypersensitivity reaction to carboplatin, pre-medication antihistamine and corticosteroids may be added

3) Etoposide therapy

i) Prehydration and post hydration not required.

ii) Give etoposide (after the carboplatin) in 50ml, 100mls or 250mls 0.9% sodium chloride (NaCl) over 1 hour.

REFERENCES:

1. Chantada,G et al, *Recommendations for Graduated-Intensity treatment of retinoblastoma in developing countries*, Pediatric Blood and Cancer, May 2013; 60 (5):719-727SIOP-PODC
2. Chantada,G et al, *A proposal for an international retinoblastoma staging system*, Pediatric Blood and Cancer, November 2006;47 (6):801-805
3. Murphree,LA et al, *Intraocular retinoblastoma: the case for a new group classification*, Opthalmol Clin North America 2005;18(1):41-53.viii

International Retinoblastoma Staging System (IRSS) [2]

Stage 0	Patients treated conservatively
Stage I	Eye enucleated, completely resected histologically
Stage II	Eye enucleated, microscopic residual tumour
Stage III	Regional extension a. Overt orbital disease b. Preauricular or cervical lymph node extension
Stage IV	Metastatic disease a. Haematogenous metastasis (without CNS involvement) 1. Single lesion 2. Multiple lesions b. CNS extension (with or without any other site of regional or metastatic disease) 1. Prechiasmatic lesion 2. CNS mass 3. Leptomenigeal and CSF disease

International Classification of Retinoblastoma (ICRB) [3]

Group A – very low risk	Eyes with small discrete tumours away from critical structures All tumours are 3 mm or smaller, confined to the retina, and located at least 3 mm from the foveola and 11.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed
Group B – low risk	Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location Retinal tumours may be of any size or location not in Group A. No vitreous or subretinal seeding allowed, A small cuff of subretinal fluid extending no more than 5 mm from the base of the tumour is allowed.
Group C – moderate risk	Eyes with only focal vitreous or subretinal seeding and discrete retinal tumours of any size and location. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Retinal tumours are discrete and of any size and location. Up to one quadrant of subretinal fluid may be present.
Group D – high risk	Eyes withy diffuse vitreous or subretinal seeding an/or massive, nondiscrete endophytic or exophytic disease Eyes with more extensive seeding than Group C. Massive and/or diffuse intraocular disseminated disease may consist of fine or "greasy" vitreous seeding or avascular masses. Subretinal seeding may be plaque-like. Includes exophytic disease and more than one quadrant of retinal detachment.
Group E – very high risk eyes	Eyes that have been destroyed anatomically or functionally by the tumour. Eyes with one or more of the following: Irreversible neovascular glaucoma, massive intraocular haemorrhage, aseptic orbital cellulitis, tumour anterior to the anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma, phthisis and pre-phthisis.

SURNAME _____ NHI :_____

FIRST _____

DOB: ___/___/___ SEX _____

Please attach patient label here

National Child Cancer Network NZ
Linking Care / Sharing Knowledge / Advancing Best Practice

PI Protocol

PI Retinoblastoma (PI RET-1)
Carboplatin + Etoposide + Vincristine
Cycle:_____

Hypersensitivities	Treatment Modified: Yes / No Notes:	Date: Height: cm Weight: kg BSA: m^2

Source protocol ARET0332. Each course lasts for 28 days. Start next course when neutrophils ≥ $1x10^9$/L, platelets ≥ $100x10^9$/L and haemoglobin > 80 g/L.

Date	Time	Medication	Dose	Units	Route	Administration/Fluid	Rate	Administration Date	Time	Dose	Given By	Check
Day 1 Neut:____ x10^9/L Plts:____x10^9/L Hb:____g/L GFR:____mL/min/1.73m^2 Consultant approval to start chemotherapy Signed: _____ Date: …./…./….												
	T=0	**Vincristine** 0.05mg/kg if < 36 months 1.5mg/m^2 if ≥ 36 months (max 2mg)		mg	IV	Push	Over 1 minute					
		Carboplatin 18.6mg/kg if < 36 months 560mg/m^2 if ≥ 36 months		mg	IV	In 50mL or 100mL glucose 5% (please circle fluid volume)	Over 1 hour					
	T+1	**Etoposide** 5mg/kg if < 36 months 150mg/m^2 if ≥ 36 months		mg	IV	In 50mL or 100mL or 250mL NaCl 0.9% (please circle fluid volume)	Over 1 hour					
Day 2												
	T=0	**Etoposide** 5mg/kg if < 36 months 150mg/m^2 if ≥ 36 months		mg	IV	In 50mL or 100mL or 250mL NaCl 0.9% (please circle fluid volume)	Over 1 hour					

Prescribing Doctor Signature:_____ Prescribing Doctor Name: _____ Date:_____

NaCl = Sodium chloride

Specimen Signatures (name and initials):	Pharmacy use:	Supportive care: ☐ PCP prophylaxis – Cotrimoxazole BD Sat and Sun ☐ Antiemetic grading -