WILMS TUMOUR

PI Wilms-1 Protocol

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WILMS TUMOUR PROTOCOL – PI WT #1

Source-National Wilms Tumour Study – 5 (NWTS-5)
and for Fiji SIOP Umbrella Study 2016.

1.0 BACKGROUND

Wilms tumour is the most frequent malignant renal tumour in children., and accounts for 6-8% of paediatric malignancies.
In 1969, the paediatric divisions of two cooperative groups Acute Leukaemia Group B and the Southwest Cancer Chemotherapy Group, the Children's Cancer Study Group and several independent institutions joined together to form the National Wilms Tumour Study (NWTS) Group. Four clinical trials have been completed.
As the result of these studies, the survival rate of children with Wilms tumour has risen from 20% two years after diagnosis to 90% two years after diagnosis. This success has been the result of collaborative efforts among surgeons, paediatricians, pathologists and radiation oncologists. Prompt surgical excision of the renal tumour, followed by post-operative radiation therapy, as indicated, and adjuvant chemotherapy have contributed to these good results.
The major conclusions of National Wilms Tumour Studies - 1, - 2 and - 3 are:
1) routine, postoperative radiation therapy of the flank is not necessary for children with stage I/favourable histology or stage I/anaplastic tumours, or for those with stage

II/favourable histology tumours, when post-nephrectomy combination chemotherapy consisting of vincristine and dactinomycin is administered;
2) the prognosis for patients with stage III/favourable histology patients is best when the treatment program includes either:
(i) dactinomycin + vincristine + doxorubicin + 1000 cGy radiation therapy to the flank; or
(ii) dactinomycin + vincristine + 2000 cGy radiation therapy to the flank;
3) the addition of cyclophosphamide to the combination of vincristine +dactinomycin + doxorubicin did not improve the prognosis for patients with stage IV/favourable histology tumours.

At the present time, some patients with favourable histology Wilms tumour who will relapse can be identified at the time of diagnosis on the basis of demographic variables, such as age at diagnosis, or staging variables such as lymph node involvement, local or intravascular tumour extension.

For Fiji, the International Society of Paediatric Oncology (SIOP) approach is preferred. This differs from the Children's Oncology Group approach largely by recommending chemotherapy on the basis of a radiologically confirmed renal tumour. By giving chemotherapy before nephrectomy, the surgical procedure is safer with reduced risk of intra-operative rupture. This is followed by nephrectomy and post-operative treatment based on stage, histology and for Intermediate Risk, the size of the tumour. In many respects, the results of the COG and SIOP approach are very similar.

STAGE V (BILATERAL) WILMS TUMOUR
Patients who present with bilateral Wilms tumour (stage V) account for approximately five percent of all children with Wilms tumour. Reviews of the outcome of these children on the NWTS have indicated that they have an excellent prognosis, with survival rates for those having favourable histology exceeding 80% at two years and 70% at ten years after diagnosis. Concerns regarding the impact of hyperfiltration injury on patients with less than 50% of their renal parenchyma remaining after surgery, and the presence of renal failure in 5.4% of long-term survivors of bilateral Wilms tumour have resulted in a more conservative surgical approach to these patients without a decrease in survival percentages.

PRE-NEPHRECTOMY CHEMOTHERAPY
Patients with intravascular extension of Wilms tumour into the vena cava have at least stage II Wilms tumour. Primary surgical removal of tumours with intracaval extension is associated with an increased incidence of surgical complications. This is particularly true for those patients with intracaval extension above the level of the hepatic veins or even further into the right atrium. These extensive tumours can be managed with preoperative chemotherapy to facilitate shrinkage of the intravascular thrombus.
This approach will facilitate subsequent surgical removal.

2.0 TREATMENT PLAN- Country specific.
Fiji:

- See appendix II

Tonga, Samoa and Vanuatu:

- On imaging suspicion of Wilms tumour, arrange transfer to Starship, Auckland, NZ as soon as feasible.
- Decision will then be made whether nephrectomy possible.
- If up front nephrectomy, post-operative chemotherapy dependent on stage.
- If inoperable pre-operative chemotherapy (VCR/ACT-D +/-DOXO) given, then reimage week 5 with surgery at week 6.
- To return to island of referral, once clinically stable from nephrectomy and initial chemotherapy (either VCR/ACT-D or VCR/ACT-D/DOXO) and completion of radiotherapy (if indicated)

3.0 AGENT INFORMATION

3.1 **DACTINOMYCIN (Actinomycin-D, Cosmegen)**
3.11 **Source and Pharmacology**: Derived from Streptomyces parvullus. Intercalates with DNA, inhibiting DNA-dependent RNA polymerase and, at high concentrations, prevents DNA replication. It is phase specific, primarily to the G, and S phases. It has a very short initial plasma half-life of 1 minute but a prolonged terminal plasma half-life of 36 hours. It is excreted primarily by the liver. Very little diffusion occurs into the CSF.
3.12 **Toxicity:** Acute DLT - myelosuppression with a nadir of 2-3 weeks, and also, possibly severe diarrhoea with a nadir of 2-3 days. Other side effects include nausea and vomiting, alopecia, immunosuppression, local ulceration after extravasation, and mucosal ulceration (rare). Life-threatening hepatic toxicity occurs in approximately 3.5% of patients given vincristine and dactinomycin in combination. The agent is a radiosensitizer and will enhance radiotherapy damage, especially with concomitant radiotherapy. Toxicity may be enhanced by liver damage, especially with concomitant radiotherapy to the liver.
3.13 **Formulation and Stability:** Lyophilized powder, in vials containing 500mcg of dactinomycin, with 20mg of mannitol. Store at room temperature. Reconstitute using 1.1ml sterile water without preservative. Stable at room temperature, but protect from light. Use within 24 hours.
3.14 **Guides for Administration:** IV push over 1 minute or less.
Special Precautions: -
Flush vein before and after infusion.
Avoid extravasation or local contact with skin or conjunctiva.
3.15 **Supplier:** Commercially available. See package insert for further information.

3.2 **DOXORUBICIN (Adriamycin)**
3.21 **Source and Pharmacology:** An anthracycline antibiotic isolated from cultures of Streptomyces peucetius. Binds to DNA and inhibits nucleic acid synthesis, with its major lethal effect occurring during the S phase of the cell cycle. Has some topoisomerase II inhibitory activity. Since it is primarily excreted by the liver, any liver impairment may enhance toxicity. 40% to 50% is excreted in the bile; <5% in

the urine. The drug has a very short initial t½ of <20 minutes and a terminal t½ of 17 hours. Animal studies indicate cytotoxic levels persist in tissue for as long as 24 hours.

3.22 **Toxicity:** Acute DLT is myelosuppression, mainly leucopoenia, with a nadir of 1-2 weeks. Thrombocytopenia may also occur. Toxicity may be enhanced by significant liver or renal dysfunction, since it is primarily excreted by these organs. If the serum bilirubin is 1.2-3mg/dl, it is recommended that the dose should be reduced by 25%; >3 mg/dl reduce to 50%. It is a radiosensitizer and may enhance radiotherapy damage. It may cause cardiac arrhythmias immediately following administration. Other adverse reactions include immunosuppression, nausea and vomiting, stomatitis, alopecia, and ulceration secondary to local extravasation. Red coloured urine is not a toxic effect. Has more GI toxicity than daunorubicin. Chronic DLT (total dose >200mg/M_2) is cardiac toxicity manifested by decreased contractility which may progress to congestive heart failure. The long-term reversibility of the cardiomyopathy is unknown. Cardiac toxicity is enhanced by cardiac irradiation. Note that doxorubicin augments radiotherapy damage.

Patient should have baseline monitoring of cardiac function (ECG, echocardiogram) prior to receiving doxorubicin, followed by monitoring as indicated.

If there is any evidence of cardiomyopathy, stopping of therapy should be considered. If clinical signs of heart failure occur, therapy should be stopped permanently.

After cessation of therapy and anthracycline doses of >200mg/M_2, cardiac evaluation should be done every three – five years, and during marked increase in physiologic stress (e.g., pregnancy).

3.23 **Formulation and Stability:** Available as a freeze-dried powder in 10mg, 20mg, 50mg, 100mg and 150mg vials. Store at room temperature. Also available as 2 mg/ml solution in 5ml(10 mg), 10ml(20mg), 25ml(50mg) and 100ml(200mg) multidose vials. Store refrigerated. Reconstitute the powdered form with normal saline, so that there is 2mg/ml; refrigerate, protect from light and prolonged exposure to aluminium. See package insert for storage temperatures and stabilities.

3.24 **Guidelines for Administration and Follow-Up:**

IV infusion over 5 minutes or more, in a well-established line.

Special Precautions: Avoid extravasation and local contact with skin or conjunctiva. Avoid mixing with other agents, especially heparin.

Dose modification may be indicated with impaired liver function (See toxicity).

3.25 **Discontinuation of Anthracycline Therapy:** Anthracycline therapy should be discontinued if clinical signs of congestive heart failure occur. Unfortunately measurements of left ventricular function do not predict which patients will develop congestive heart failure.

3.3 **VINCRISTINE SULFATE (VCR, Oncovin)**

3.31 **Source and Pharmacology:** Vincristine is an alkaloid isolated from Vinca rosea (periwinkle). It is lethal during the S phase and binds microtubules causing arrest of cell division in metaphase binder. Its serum decay pattern is triphasic, with initial, middle and terminal half-lives of 5 minutes, 1.3 hours, and 85 minutes, respectively. It is excreted in the bile and faeces. There is poor CSF penetration.

3.32 **Toxicity:** Acute DLT is due to reversible peripheral neuropathy which includes constipation and/or paralytic ileus. In the infant, ptosis and vocal cord paralysis and weakness may occur. Other signs and symptoms of peripheral neuropathy include jaw pain, and loss of deep tendon reflexes. Other adverse reactions include minimal myelosuppression, immunosuppression, alopecia, rare CNS depression, syndrome of inappropriate ADH secretion (SIADH), convulsions, and ulceration secondary to local extravasation. Note: Liver dysfunction may enhance toxicity.
3.33 **Formulation and Stability:** Available in solutions of 1mg/1ml in 1ml, 2ml, or 5ml vials. Refrigerate and protect from light. Once opened, it should be refrigerated and used within 10 days. Note: The drug is light-sensitive.
3.34 **Guidelines for Administration:** IV push over <1 minute.
Special Precautions: Avoid extravasation.
Precaution: Concomitant radiation therapy to the liver may enhance toxicity.
3.35 **Supplier:** Commercially available. See package insert for further information.

4.0 PATHOLOGY

Fiji: pathological review of specimens by CHOC, Christchurch or Starship, Auckland, NZ. (logistics of transportation of slides to be discussed)

NZ: As per institutional best practice – to define subtype of Wilms

- Favourable/unfavourable
- Anaplasia- focal/diffuse
- Presence or absence of nephrogenic rests

5.0 STAGING

The following staging system applies to all tumours.
For Fiji staging (except for the definition of metastatic stage IV disease or bilateral stage V disease) is not completed until after tumour resection.

5.1 Stage I - The tumour is limited to the kidney and was completely resected. The renal capsule has an intact outer surface. The tumour was not ruptured or biopsied prior to removal. **The vessels of the renal sinus are not involved.** There is no evidence of tumour at or beyond the margins of resection.
5.2 Stage II - The tumour extends beyond the kidney, but was completely resected. There is regional extension of tumour (i.e., penetration of the renal capsule, or **extensive invasion of the renal sinus.** The blood vessels outside the renal parenchyma, including those of the renal sinus, contain tumour. The tumour was biopsied (except for fine needle aspiration), or there was spillage of tumour before or during surgery that is confined to the flank, and does not involve the peritoneal surface. There is no evidence of tumour at or beyond the margins of resection.
5.3 Stage III - Residual non-haematogenous tumour is present, and confined to the abdomen. Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are found to be
- involved by tumour (renal hilar, para-aortic or beyond). **(Lymph node involvement in the thorax, or other extra-abdominal sites would be a criterion for stage IV).**

- The tumour has penetrated through the peritoneal surface.
- Tumour implants are found on the peritoneal surface.
- Gross or microscopic tumour remains post-operatively (e.g., tumour cells are found at the margin of surgical resection on microscopic examination).
- The tumour is not completely resectable because of local infiltration into vital structures.
- Tumour spill not confined to the flank occurred either before or during surgery.

5.4 Stage IV - Haematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdomino-pelvic region are present.
Pulmonary nodules not detected on chest radiographs but visible on computerized tomography of the chest (so-called "CT only" metastases) do not mandate treatment with whole lung irradiation. Required treatment of such patients is according to the stage of the renal tumour.
5.5 Stage V - Bilateral renal involvement is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease prior to biopsy.

6.0 PRE-TREATMENT EVALUATION

6.1 History - Note history of pre-existing and non-infectious disease, details regarding the diagnosis of Wilms tumour in any relative, and the family history of cancer, congenital defects, and benign tumours.
6.2 Physical Examination - Include a measurement of blood pressure, weight, height, size of the liver and spleen, the presence of palpable lymph nodes, and the site and size of the abdominal mass(es). Record the presence of any congenital anomalies, noting specifically the presence or absence of hemihypertrophy, genitourinary anomalies, anomalies associated with the Beckwith-Wiedemann syndrome (BWS) and aniridia.
6.3 Laboratory Investigations:

- FBC-Haemoglobin, white blood cell count, differential and platelet count.
- Urinalysis, noting the presence or absence of protein, white and/or red blood cells.
- Blood chemistries – sodium, potassium, urea, creatinine, liver function, and albumin.

6.4 Radiologic Examinations - These are designed to:
(1) establish the presence of a functioning, normal contralateral kidney;
(2) establish that the renal vein and inferior vena cava are free of tumour thrombi; and
(3) establish that there are no pulmonary metastases. The following are the minimum requirements to establish these points:

- PA and lateral views of the chest.
- Computed tomography scan of the chest.
- Abdominal ultrasound - This study is performed to determine if the abdominal tumour is solid or cystic. This study has been very useful in the preoperative detection of tumour thrombi in the renal vein, inferior vena cava and right atrium.
- Computed tomography scan of the abdomen.

7.0 REGISTRATION

Upon diagnosis all patients with Wilms will be recorded on the unit registry and in time on the Pacific Children's Cancer Registry (PCCR).

8.0 EVALUATIONS DURING AND FOLLOWING THERAPY

8.10 **Evaluations During Therapy – Tonga, Samoa and Vanuatu**

Regimen EE-4A

WEEK	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**
HX/PE	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
FBC*	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
LFTs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Urea	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Creatinine	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Urinalysis	**x**							**x**
CXR	**x**		**x**					**x**
Abd US	**x**		**x**					**x**
CT chest #	**x**							
CT abdomen #								

* weekly till week 10

Regimen DD-4A

WEEK	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**
HX/PE	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
FBC *	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
LFTs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Urea	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Creatinine	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Urinalysis	**x**									**x**
CXR ^	**x**									**x**
Abd US ^	**x**									**x**
CT chest #	**x**									
CT abd #										
ECHO ^	**x**									**x**

***** weekly till week 10

If inoperable: re- evaluate at week 5 with CT chest/abdomen prior to surgery week 6
^ As clinically indicated

8.20 **Examinations After Completion of Therapy**

The ethical question is, if there is no treatment for relapsed disease, what is the value of imaging surveillance?

Recommend imaging CXR/US abdomen or CT scan as clinically indicated.

However, if patient young (<12 months) or if presence of predisposing condition such as BWS there is a greater chance of bilateral disease:
- either at presentation (synchronous Wilms)
or
- off therapy (metachronous Wilms).
In such situations imaging surveillance off therapy indicated.

8.21 **Late Effects Surveillance:**

- Single kidney guidelines- avoid contact sports (refer Children's Oncology Group guidelines : *survivorshipguidelines.org*)
- Monitor urine for evidence hyperfiltration injury-dipstix for protein
- Monitor blood pressure
- Echocardiogram for those exposed to Anthracycline (Doxorubicin)

9.0 TREATMENT PLAN AND MODIFICATIONS (See Appendix I for Schemas)

9.1 **CHEMOTHERAPY GUIDELINES – Tonga, Samoa and Vanuatu**
(For Fiji see appendix II)
Note: The day of nephrectomy will be considered day 0; the first dose of chemotherapy will be measured in days from that starting point.
No dose of dactinomycin or doxorubicin should be initiated if the absolute neutrophil count is < 1,000/mm^3 or the platelet count is < 100,000/mm^3.

Dose Calculations:
Babies <12 months of age should receive ONE-HALF of the recommended dose of all chemotherapeutic agents, as calculated on the basis of body weight.
Full doses of chemotherapeutic agents should be administered to these patients when the child is >12 months of age.

The treatment plan will vary by stage, age, tumour weight and/or histology as follows:

9.11 **STAGE I and II FAVORABLE HISTOLOGY and STAGE I focal or diffuse anaplasia.**

Nephrectomy, chemotherapy using Regimen EE-4A (See Section 9.111 below):
Trimethoprim (TMP)/sulfamethoxazole prophylaxis (see Appendix III)
Regular laxatives while on weekly vincristine.

9.111 **Regimen EE-4A**
(Appendix I)
Dactinomycin
Dose for children < 30kg:
0.045 mg/kg/dose IV push (maximum dose - 2.3 mg), beginning within
5 days post-nephrectomy (during week 0), and then at weeks 3, 6, 9, 12, 15, and 18.
If surgery is to be delayed commence week 0 with Dactinomycin on D1.
Dose for children >30kg:
1.35 mg/M^2 IV push, but no single dose should exceed 2.3 mg.

Vincristine
Dose for children < 30kg:
0.05 mg/kg IV push (maximum dose - 2 mg), beginning day 7 post-nephrectomy (week 1or week 0 Day 1 if surgery is to be delayed) if peristalsis has been established; then weekly for a total of 10 doses.
Then vincristine 0.067 mg/kg IV push (maximum dose - 2.0 mg) with dactinomycin at weeks 12, 15 and 18.

Dose for children >30kg:
1.5 mg/M^2 IV push (maximum dose - 2.0 mg), beginning day 7 post-nephrectomy (week 1 or week 0 D1 if surgery is to be delayed) if peristalsis has been established; then weekly for a total of 10 doses
Then vincristine 2.0 mg/M^2 IV push (maximum dose - 2.0 mg), with dactinomycin at weeks 12, 15 and 18.

9.12 **STAGE III/FAVORABLE HISTOLOGY AND STAGES II OR III/FOCAL ANAPLASIA:**
Nephrectomy, abdominal irradiation, chemotherapy using Regimen DD-4A (below):
Trimethoprim (TMP)/sulfamethoxazole prophylaxis (see Appendix III).
Regular laxatives while on weekly vincristine.

9.121 Regimen DD-4A (Appendix I)

Dactinomycin
Dose for children < 30kg:
0.045 mg/kg/dose IV push (maximum dose - 2.3 mg), beginning within
5 days post-nephrectomy (during week 0), and then at weeks 6, 12, 18, and 24.
The dose of dactinomycin administered at week 6 should be decreased by 50% (0.0225 mg/kg/dose) if whole lung or whole abdomen radiation therapy has been given.

Dose for children >30kg:
1.35 mg/M^2 IV push (maximum dose - 2.3 mg), beginning within
5 days post-nephrectomy (during week 0), and then at weeks 6, 12, 18, and 24.
The dose of dactinomycin administered at week 6 should be decreased by 50% (0.675 mg/M^2) if whole lung or whole abdomen radiation therapy has been given.

Vincristine

Dose for children < 30kg:

0.05 mg/kg IV push (maximum dose - 2 mg), beginning day 7 post nephrectomy (week 1) if peristalsis has been established, then weekly for a total of 10 doses.
Then vincristine 0.067 mg/kg IV push (maximum dose - 2 mg) with dactinomycin or doxorubicin at weeks 12, 15, 18, 21 and 24.

Dose for children >30kg:

1.5 mg/M^2 IV push (maximum dose - 2 mg), beginning day 7 post-nephrectomy (week 1) if peristalsis has been established; then weekly for a total of 10 doses
Then vincristine 2.0 mg/M^2 IV push (maximum dose - 2 mg) with dactinomycin or doxorubicin at weeks 12, 15, 18, 21 and 24.

Doxorubicin

Dose for children < 30kg:

1.5 mg/kg IV push, is given at weeks 3 and 9; then
1.0 mg/kg IV push is given at weeks 15 and 21.
The dose of doxorubicin administered at week 3 should be decreased by 50% (0.75 mg/kg) if whole lung or whole abdomen radiation therapy has been given.

Dose for children >30kg:

45 mg/M^2 IV push at weeks 3 and 9, then Doxorubicin 30 mg/M^2 IV push at weeks 15 and 21
The dose of doxorubicin administered at week 3 should be decreased by 50% (22.5 mg/M^2) if whole lung or whole abdomen radiation therapy has been given.

9.13 **STAGE IV/FAVORABLE HISTOLOGY OR FOCAL ANAPLASIA:**
Nephrectomy, abdominal irradiation according to the local stage of the renal tumour, bilateral pulmonary irradiation, chemotherapy using Regimen DD-4A (see above).
Pulmonary nodules not detected on chest radiographs but visible on computerized tomography of the chest (so-called "CT only" metastases) do not mandate treatment with whole lung irradiation.
Required treatment of such patients is according to the stage of the renal tumour.
Trimethoprim (TMP)/sulfamethoxazole prophylaxis (see Appendix III)
Regular laxatives while on weekly vincristine.

9.14 **STAGE V:** Initial bilateral tumour biopsy and treatment to be performed in New Zealand centre (section 9.3).
Re-evaluation five weeks after diagnosis. The aim is renal parenchymal sparing surgery, if possible.

9.2 **SURGICAL GUIDELINES**
Nephrectomy as per institutional guidelines/best practice.

9.3 **MANAGEMENT OF BILATERAL WILMS TUMOUR**
Discuss with treatment centre in NZ.

9.4 **INOPERABLE TUMOURS**

9.41 Tumours may be inoperable because of size, extension into the suprahepatic portion inferior vena cava, and/or other reasons.

9.411 There are occasional patients with massive tumours judged by the surgeons to pose too great a risk for surgical removal.

Past experience in the NWTSG and the studies conducted by the International Society of Paediatric Oncology (SIOP) have shown that pre-treatment with chemotherapy almost always reduces the bulk of the tumour and renders it resectable.

9.412 Patients with extension of tumour above the level of the hepatic veins have excessive surgical morbidity, and may be managed successfully with pre-nephrectomy chemotherapy.

9.42 It is recommended that patients **not** undergo initial exploration to assess operability and/or obtain a biopsy of the tumour.

9.43 These patients should be treated with Regimen DD-4A, except that the first and second doses of vincristine are given on days 0 and 7 (see section 9.121)

Once there is an adequate reduction in the size of the tumour to facilitate nephrectomy, definitive resection should be completed. In general, radiographic re-evaluation should be performed at week 5. (Expect about 60% shrinkage in size of tumour by week 5).

The operative procedure can be performed shortly thereafter (week 6) if sufficient tumour shrinkage has occurred. Failure of the tumour to shrink could be due to predominance of skeletal muscle or benign elements and a second look procedure to confirm persistent tumour may be necessary.

9.44 Following surgical resection, patients should continue on treatment as per histology.

NOTE ADMINSTRATION OF RADIOTHERAPY DEPENDENT ON: STAGE and AVAILABILITY.

9.5 **CRITERIA FOR MODIFICATION OF THERAPY**

9.51 Haematological Toxicity:

- Neutropaenia: Vincristine may be continued without regard to the ANC if the patient is clinically well.
- Thrombocytopenia: The doses of the agents should be reduced by 50% in the next course if administration of a dose/course of therapy is delayed for seven (7) or more days because the platelet count is less than 100,000/mm^3. The doses may be increased for subsequent doses/courses in increments of 25% until the 100% dose level is reached.

Pronounced, selective thrombocytopenia and signs of liver dysfunction may be seen in children given dactinomycin or doxorubicin and concurrent radiation therapy to the right hemiabdomen.

Patients on Regimen DD-4A should be monitored particularly carefully for this complication.

Subsequent courses of chemotherapy should be modified for patients experiencing this complication.

9.52 Oral ulcerations which interfere with oral fluid intake should result in a 50% decrease in the dosage of dactinomycin or doxorubicin, administered with the next dose. The dosage may then be increased in increments of 25% to 100% if subsequent doses are not associated with severe stomatitis.

9.53 Gastrointestinal Function:

- Vomiting: This should be treated with antiemetics. If vomiting is judged to be severe, requiring supplementary hydration with intravenous fluids on two successive courses of treatment, the dosage of those agents associated with vomiting may be decreased by 50%.
- Constipation: This is a common side effect of vincristine. The use of laxatives during the period of weekly vincristine administration is **mandated**. In the immediate post-operative period, vincristine should not be given until there are signs of normal bowel function. Parents should be advised of the possibility of drug-induced constipation. Vincristine should not be administered if ileus is present. If ileus was drug related, the drug should be restarted at 50% of the previous dosage. The drug dose may be increased in increments of 25% to 100% if subsequent doses do not produce severe constipation or ileus.

9.54 Peripheral neuropathy:

- Vincristine can be continued in the face of depressed or absent deep tendon reflexes, and/or moderate weakness. Painful paraesthesia's which are not controlled with non-narcotic pain medications, peripheral nerve palsies, foot drop, or cranial nerve palsies are indications for omission of one or two doses of vincristine. The drug should be restarted at 50% of the previous dose, and increased in increments of 25%, if subsequent doses are not associated with recurrence of signs of severe neuropathy.

9.55 Cardiac abnormalities:

Overt cardiac failure is an indication for permanent discontinuation of therapy with doxorubicin.

Cardiomyopathy is more likely to occur in patients who have received thoracic radiation therapy, or abdominal radiation therapy in which the left ventricle has been included in the treatment volume.

9.56 Hepatic function: The doses of vincristine, dactinomycin and doxorubicin should be modified, as shown in the Table 1 for hepatic dysfunction

Table 1

Drug Dose Modification for Hepatic Function

SGPT	TOTAL BILIRUBIN	DRUG DOSE
< 2 x normal	< 1.2 mg/dl (<24 umol/L)	100%
	1.2 - 3.0 mg/dl	75%
2-5 x normal	3.0 - 5.0 mg/dl	50%
> 5 x normal	> 5.0 mg/dl	0%

PATIENT/PARENT INFORMATION SHEET:
PI -WILMS: STAGES I-II FAVORABLE HISTOLOGY

Any treatment has potential side effects. The treatments used in this program may cause some or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.
Known side effects include:

Vincristine:

1. Hair loss. This may be partial or complete; however, hair growth usually returns when the drugs are discontinued, although it may be a slightly different colour or texture than before;
2. Anaemia (decreased production of red blood cells). Anaemia can be corrected through the use of blood transfusions;
3) Tingling of the fingers and toes;
4) Fever;
5) Muscular weakness;
6) Jaw pain;
7) Constipation with mild abdominal pain and, rarely, convulsions. Chemical burns to the skin may result if the drug leaks out of the vein during administration.
This may result in scarring. Rarely, a skin graft is needed to repair a burn caused by vincristine. This drug will be given into the vein (intravenously, IV).

Dactinomycin:

1. Bone marrow depression. The bone marrow is the site of production and development of red blood cells. Bone marrow depression results in a decreased production of red cells causing anaemia, decreased platelet production causing bruising and increased bleeding tendency, and decreased white cell production causing increased tendency to infection. Anaemia can be corrected through the use of blood transfusions; platelets may be replaced with platelet transfusions, but white cell replacement is far more difficult and an increased risk of infection usually persists for the period of low white cell count. Bone marrow depression is usually temporary;
2. Nausea and vomiting. This may cause loss of appetite;
3. Hair loss. This may be partial or complete; however, hair growth usually returns when the drugs are discontinued, although it may be a slightly different colour or texture than before;
4. Diarrhoea;
5. Sore mouth occasionally with ulcers. Rarely, dactinomycin causes serious, but temporary damage to the liver. Chemical burns to the skin may result if the drug leaks out of the vein during administration. This may result in scarring. Rarely, a skin graft is needed to repair a burn caused by dactinomycin. This drug will be given into the vein (intravenously, IV).

PATIENT/PARENT INFORMATION SHEET:
PI-WILMS:
STAGES III-IV FAVORABLE HISTOLOGY OR /FOCAL ANAPLASIA

Any treatment has potential side effects. The treatments used in this program may cause some or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.
Known side effects include:
Vincristine: 1. Hair loss. This may be partial or complete; however, hair growth usually returns when the drugs are discontinued, although it may be a slightly different colour or texture than before;
2. Anaemia (decreased production of red blood cells). Anaemia can be corrected through the use of blood transfusions;
3) Tingling of the fingers and toes;
4) Fever;
5) Muscular weakness;
6) Jaw pain;
7) Constipation with mild abdominal pain and, rarely, convulsions. Chemical burns to the skin may result if the drug leaks out of the vein during administration.
This may result in scarring. Rarely, a skin graft is needed to repair a burn caused by vincristine. This drug will be given into the vein (intravenously, IV).
Dactinomycin:
1. Bone marrow depression. The bone marrow is the site of production and development of red blood cells. Bone marrow depression results in a decreased production of red cells causing anaemia, decreased platelet production causing bruising and increased bleeding tendency, and decreased white cell production causing increased tendency to infection. Anaemia can be corrected through the use of blood transfusions; platelets may be replaced with platelet transfusions, but white cell replacement is far more difficult and an increased risk of infection usually persists for the period of low white cell count. Bone marrow depression is usually temporary;
2. Nausea and vomiting. This may cause loss of appetite;
3. Hair loss. This may be partial or complete; however, hair
growth usually returns when the drugs are discontinued, although it may be a slightly different colour or texture than before;
4. Diarrhoea;
5. Sore mouth occasionally with ulcers. Rarely, dactinomycin causes serious, but temporary damage to the liver. Chemical burns to the skin may result if the drug leaks out of the vein during administration. This may result in scarring. Rarely, a skin graft is needed to repair a burn caused by dactinomycin. This drug will be given into the vein (intravenously, IV).
Doxorubicin:
1. Nausea and vomiting. This may cause loss of appetite;
2. Bone marrow depression. The bone marrow is the site of production and development of red blood cells. Bone marrow depression results in a decreased production of red cells causing anaemia, decreased platelet production causing bruising and increased

bleeding tendency, and decreased white cell production causing increased tendency to infection. Anaemia can be corrected through the use of blood transfusions; platelets may be replaced with platelet transfusions, but white cell replacement is far more difficult and an increased risk of infection usually persists for the period of low white cell count. Bone marrow depression is usually temporary;
3) Hair loss. This may be partial or complete; however, hair growth usually returns when the drugs are discontinued, although it may be a slightly different colour or texture than before:
4) Mouth ulcers;
5) Damage to heart muscle after prolonged treatment. Chemical burns may result if the drug leaks out of the vein during administration. This may result in scarring. Rarely, a skin graft is needed to repair a burn caused by doxorubicin. This drug will be given into the vein (intravenously, IV).

APPENDIX I

PI- WILMS TUMOUR #1

STAGE I/IIFAVORABLE HISTOLOGY

REGIMEN EE-4A

WEEK 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

A A A A A A A

VVV VV V VV V V V* V* V*

A - DACTINOMYCIN (45 MCG/KG, IV)
V - VINCRISTINE (0.05 MG/KG, IV)
V* - VINCRISTINE (0.067 MG/KG, IV)

STAGE III AND IV/FAVORABLE HISTOLOGY OR FOCAL ANAPLASIA

REGIMEN DD-4A

WEEK 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

A D+ A D+ A D* A D* A

VVV VV VV V V V V* V* V* V* V*

XRT

A – DACTINOMYCIN (45 MCG/KG, IV)
D* - DOXORUBICIN (1.0 MG/KG, IV)
D+ - DOXORUBICIN (1.5 MG/KG, IV)
V – VINCRISTINE (0.05 MG/KG, IV)
V* - VINCRISTINE (0.067 MG/KG, IV)
XRT - RADIATION THERAPY

APPENDIX II

Treatment of Wilms Tumour – Fiji (adapted from SIOP Umbrella Protocol 2016)

The principle with this approach is to deliver pre-nephrectomy chemotherapy to children with a CT-identified renal tumour with the likelihood (85%) of a diagnosis of Favourable Histology Wilms tumour. This approach holds 3 advantages:

1. Reduces the risk of intra-operative tumour rupture
2. Buys time for the surgeons to organise the nephrectomy
3. Explores chemosensitivity – sensitive tumours may be allocated a lower risk group on the basis of down-staging, volume reduction and/or histological response

Staging and risk grouping (except for stage IV – lung metastases) is not known until histology is reported.

Localised Unilateral Renal Tumour

Because of a greater chance of non-Wilms tumour in young infants – mesoblastic nephroma, rhabdoid tumour - immediate nephrectomy should be performed on patients < 7 months of age.

Pre-operative Chemotherapy

For children ≥ 7 months of age - deliver vincristine and actinomycin-D for 4 weeks followed by nephrectomy at week 5 or 6. If surgery is planned for week 6, deliver an additional vincristine on week 5 - (↓) below. Plan nephrectomy with the surgeon at the commencement of treatment. Repeat abdominal CT at week 4 or 5 to assist the surgeon in planning nephrectomy.

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓		↓				
Vincristine 1.5mg/m^{2*} IV bolus (max dose 2mg)	↓	↓	↓	↓	(↓)		
CT abdomen				↓	(↓)		
Surgery						↓	(↓)
Week	1	2	3	4	5	6	

*Dose modifications:

<12 kg – give 66% of dose
< 6 months – give 50% of dose

Post-operative therapy

The combination and duration of chemo- and radiotherapy is based the following 3 criteria:

1. Staging – see section 5
2. Tumour volume > or < 500mls – *Intermediate Risk only*

3. Histology of the resected kidney:

Low Risk
Completely (100%) necrotic

Intermediate Risk
All remaining Wilms tumours

High Risk
Wilms tumour : Diffuse anaplasia
Non-Wilms tumours: Rhabdoid tumour
Clear cell sarcoma

Deliver post-operative treatment according to this table:

	Specific variables	**Stage I**	**Stage II**	**Stage III**
Low risk histology	All	No further treatment	AV2	AV2
Intermediate risk histology	Volume ≤ 500mls	AV1	AV2	AV2 + flank radiation
	Volume > 500mls	AV1	AVD	AVD + flank radiation
High risk histology	Diffuse anaplasia	AVD	Discuss with CHOC	Discuss with CHOC
	Non-Wilms tumours	Discuss with CHOC	Discuss with CHOC	Discuss with CHOC

Regimen AV1

Give the 1st post-operative dose of vincristine once peristalsis is established, at least within 3 weeks of the last pre-operative chemotherapy.
Check blood counts weekly – continue with vincristine if clinically well but delay actinomycin-D if

- neutrophils < $1000x10^6$/L or
- platelets < $100,000x10^6$/L

Actinomycin-D 45µg/kg* ↓
IV bolus (max dose 2mg)

Vincristine 1.5mg/m2* ↓ ↓ ↓ ↓
IV bolus (max dose 2mg)

Week 1 2 3 4

*Dose modifications:

<12 kg – give 66% of dose

< 6 months – give 50% of dose

Regimen AV2

Give the 1st post-operative dose of vincristine once peristalsis is established, at least within 3 weeks of the last pre-operative chemotherapy.
Check blood counts weekly – continue with vincristine if clinically well but delay actinomycin-D only up to week 11; from week 14 – 26 delay both vincristine and actinomycin-D if:

- neutrophils < $1000x10^6$/L or
- platelets < $100,000x10^6$/L

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓				↓			↓	
Vincristine 1.5mg/m²* IV bolus (max dose 2mg)	↓	↓	↓	↓	↓	↓	↓	↓	
Radiotherapy§				↓↓↓↓↓↓↓					
Week	1	2	3	4	5	6	7	8	9	10

Followed by:

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓			↓		
Vincristine 1.5mg/m²* IV bolus (max dose 2mg)	↓	↓		↓	↓	
Week	11	12	13	14	15	16
	17	18	19	20	21	22
	23	24	25	26	27	28

*Dose modifications:

<12 kg – give 66% of dose

< 6 months – give 50% of dose

§ Radiotherapy for Intermediate Risk stage III volume ≤ 500mls *only*.
Reduce dose of actinomycin-D by ⅓ if delivered within 14 days of radiotherapy

Regimen AVD

Give the 1st post-operative dose of vincristine once peristalsis is established, at least within 3 weeks of the last pre-operative chemotherapy.
Check blood counts weekly – continue with vincristine if clinically well but delay actinomycin-D and doxorubicin if:

- neutrophils < $1000x10^6$/L or
- platelets < $100,000x10^6$/L

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓				↓				↓
Vincristine 1.5mg/m^{2*} IV bolus (max dose 2mg)	↓	↓	↓	↓	↓	↓	↓	↓	↓
Doxorubicin 50mg/m^2 IV infusion over 2 hours	↓								↓
Radiotherapy§				↓↓↓↓↓↓↓					
Week	1	2	3	4	5	6	7	8	9	10

Followed by:

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓			↓		
Vincristine 1.5mg/m^{2*} IV bolus (max dose 2mg)	↓	↓		↓	↓	
Doxorubicin 50mg/m^2 IV infusion over 2 hours				↓		

Week	11	12	13	14	15	16
	17	18	19	20	21	22
	23	24	25	26	27	28

*Dose modifications:
<12 kg – give 66% of dose
< 6 months – give 50% of dose

§ Radiotherapy for Intermediate Risk stage III volume > 500mls *only.*
Reduce dose of actinomycin-D by ⅓ if delivered within 14 days of radiotherapy
Reschedule doxorubicin so that it is not delivered within 14 days of radiotherapy

Unilateral Renal Tumour with Lung Metastases – low and intermediate risk histology only

Deliver vincristine, actinomycin-D and doxorubicin for 7 weeks followed by nephrectomy at week 8. Plan nephrectomy with the surgeon at the commencement of treatment. Plan possibility of radiotherapy with CHOC:

- CHOC to provide letter justifying possibility of radiotherapy in situation of detectable but responding lung metastases at 7 weeks, or high resolution chest CT

and possible radiotherapy in case of undetectable lung metastases at 7 weeks on Fiji CT scan

- Fiji to submit for recommendation by MoH Committee which in turn seeks approval from Pacific Development, CMDHB

Repeat abdominal and chest CT at week 7 to assist the surgeon in planning nephrectomy, and determining response of the lung nodules.

Pre-operative therapy

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓		↓		↓		
Vincristine 1.5mg/m^{2*} IV bolus (max dose 2mg)	↓	↓	↓	↓	↓	↓	↓
Doxorubicin 50mg/m^2 IV bolus	↓				↓		
CT abdomen + chest							↓
Surgery ↓							
Week	1	2	3	4	5	6	7	8

*Dose modifications:

<12 kg – give 66% of dose

< 6 months – give 50% of dose

Check blood counts weekly – continue with vincristine if clinically well but delay actinomycin-D and doxorubicin if:

- neutrophils < 1000x10^6/L or
- platelets < 100,000x10^6/L

Post-operative therapy

The combination and duration of chemo- and radiotherapy is based the following 3 criteria:

1. Local Staging – see section 5; flank radiotherapy is delivered to local stage III Intermediate risk histology
2. Histology of the resected kidney – ongoing therapy will only be offered to those with Low and Intermediate risk histology
3. Response of the lung metastases:
    a. Lung metastases undetectable on Fiji CT – refer to CHOC for high-resolution chest CT and, if detectable, immediate radiotherapy to follow

b. Lung metastases detectable but >30% volume reduction – refer to CHOC for radiotherapy
c. if <30% estimated reduction in volume of metastases, discuss with CHOC

Give the 1st post-operative dose of vincristine once peristalsis is established, at least within 3 weeks of the last pre-operative chemotherapy.
Check blood counts weekly – continue with vincristine if clinically well but delay actinomycin-D and doxorubicin if:

- neutrophils < $1000x10^6$/L or
- platelets < $100,000x10^6$/L

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)	↓				↓			↓	
Vincristine 1.5mg/m²* IV bolus (max dose 2mg)	↓	↓	↓	↓	↓	↓	↓	↓	
Doxorubicin 50mg/m² IV infusion over 2 hours	↓								
Radiotherapy§					↓↓↓↓↓↓↓				
Week	1	2	3	4	5	6	7	8	9	10

Followed by:

Actinomycin-D 45µg/kg* IV bolus (max dose 2mg)			↓			↓				
Vincristine 1.5mg/m²* IV bolus (max dose 2mg)			↓	↓		↓	↓			
Week			11	12	13	14	15	16		
			17	18	19	20	21	22		
			23	24	25	26				

*Dose modifications:
<12 kg – give 66% of dose
< 6 months – give 50% of dose
§Reduce dose of actinomycin-D by ⅓ if delivered within 14 days of radiotherapy
Reschedule doxorubicin so that it is not delivered within 14 days of radiotherapy

Special Circumstances

Under particular circumstances other than presence of lung metastases, it may be inadvisable to proceed to nephrectomy at 5 (or 6) weeks, for example:

- renal tumour with extensive locoregional extension that is responding well to pre-nephrectomy chemotherapy at week 4 (or 5) but exhibits extrarenal extension

which may render surgery difficult eg. IVC, intrahepatic, cardiac extension. Under this circumstance, consider pre-nephrectomy chemotherapy as for Wilm's tumour with pulmonary metastases (AVD)

- any circumstance where surgery at week 5 (or 6) week heightens the risk of significant complication. Continue according to AV1, reimage week 8 and nephrectomy week 9

APPENDIX III

***Pneumocystis* prophylaxis**

All patients should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ). 2.5 mg/kg TMP bid (5mg/kg/day) on three consecutive days per week from the start of therapy, continuing for six months after chemotherapy is complete.

Cotrimoxazole Liquid (240mg/mL) Dose - Twice Daily on 3 days/week			
Weight of Patient (kg)	**Suspension 240mg/5ml**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
3 to 3.9	**1mL**	48	8
4 to 5.5	**1.5mL**	72	12
5.6 to 7	**2mL**	96	16
7.1 to 8.8	**2.5mL**	120	20
8.9 to 10.4	**3mL**	144	24
10.5 to 12	**3.5mL**	168	28
12.1 to 13.6	**4mL**	192	32
13.7 to 15.2	**4.5mL**	216	36
15.3 to 16.8	**5mL**	240	40
16.9 to 18.4	**5.5mL**	264	44
18.5 to 20	**6mL**	288	48
20.1 to 21.6	**6.5mL**	312	52
21.7 to 23.2	**7mL**	336	56
23.3 to 24.8	**7.5mL**	360	60
24.9 to 26.4	**8mL**	384	64
26.5 to 28	**8.5mL**	408	68
28.1 to 29.6	**9mL**	432	72
29.7 to 31.2	**9.5mL**	456	76
31.3 to 32.8	**10mL**	480	80

Cotrimoxazole tablet (480mg) Dose - Twice Daily on 3 days/week			
Weight of Patient (kg)	**480mg tablet**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
15 to 22.5	**½ tablet**	240	40
22.6 to 37.5	**1 tablet**	480	80
37.6 to 52.5	**1 ½ tablets**	720	120
> 52.6	**2 tablets**	960	160