SIOP PODC WILMS TUMOUR-1 Protocol

A SIOP PODC Level 1 protocol and guideline for the treatment of Wilms Tumour in Children

Adapted for Papua New Guinea

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Background

Incidence and Epidemiology.

- Wilms tumour comprises 6 % of childhood cancers in the United States and represents 90 % of renal tumours in children.
- Mean age of presentation 3- 4 years.
- 2-4 % of Wilms are associated with congenital syndromes.
 - (1%) WAGR syndrome (Wilms tumour, Aniridia, Genitourinary malformation, mental retardation)
 - Denys-Drash Syndrome (pseudo-hermaphroditism, degenerative renal diseaseglomerulonephritis, nephrotic syndrome)
 - (5-10%) Beckwith- Wiedemann syndrome (macroglossia, omphalocele, viceromegaly with or without hemi-hypertrophy.

No significant correlations between environmental exposures of patients or their parents and Wilms tumour. Molecular Biology

- Several genetic events contribute to Wilms tumorigenesis.
- WT1 was the first identified gene in Wilms tumour and remains the only one fully characterised.
- WT1 is found on chromosome 11p13.
- WT1 regulates the expression of other genes, many of which are involved in cell growth, differentiation and apoptosis.
- Other genes found to be associated are: WT1, IGF2 and those associated with P53.

Pathology

- Most Wilms tumours are unilateral, 7% bilateral, 12% multifocal.
- Macroscopically -Usually sharply demarcated, spherical masses with a "pushing border" relative to the renal parenchyma and a fibrous pseudo-capsule. This differentiates it from other renal tumours which have infiltrative borders.
- Microscopically consists of varying proportions of 3 main cell types; blastemal, stromal, epithelial, not all tumours contain all 3 cells.
- Monophasic blastemal tumours have to be differentiated from small round blue cell tumours (neuroblastoma, primitive neuro-epithelial tumour and lymphoma)
- Monophasic undifferentiated stromal tumours should be differentiated from primary sarcomas (clear cell sarcoma of the kidney, congenital mesoblastic nephroma, synovial sarcoma
- Purely tubular and papillary variants may be difficult to differentiate from papillary renal cell carcinoma and metanephric adenoma.
- Absence of anaplastic nuclear changes allows classification of Wilms tumour as favourable histology.
- Anaplasia- may be focal or diffuse, characterised by the presence of markedly enlarged nuclei with diameter of up to 3x that of the neighbouring cells and the presence of multipolar or obviously polypoid mitotic figures.
- Focal anaplasia is restricted to circumscribed regions of the tumour, while diffuse anaplasia is when anaplastic areas are not circumscribed or in an extra renal site.

Differential diagnosis –

1. Clear cell sarcoma of the kidneys

- 2. Rhabdoid tumour of the kidney,
- 3. Renal cell carcinoma.

SIOP PODC lists minimal requirements for treatment with curative intent

- 1. Basic lab services FBE, MPS, and HIV. Stool MCS, urinary microscopy.
- 2. Basic radiology CXR, USS
- 3. Chemotherapy drugs vincristine, actinomycin D doxorubicin and expertise and facilities foe safe administration.
- 4. Supportive care: safe blood transfusions, IV broad spectrum antibiotics, adequate pain medication and adequate nursing care.
- 5. Appropriately trained surgeon, adequate surgical surgical facilities and staff for perioperative care.
- 6. Free medical treatment and social support for impoverished families to enable parents s to complete treatment

(PODC, Paediatric Blood cancer)

Clinical presentation

- Most children are well at presentation with an abdominal mass.
- Abdominal pain, gross/ microscopic haematuria, fever, hypertension.

Examination

- Non-tender distinct flank mass, uncommonly crossing the midline
- Specifically note Wilms tumour associated syndromes (WAGR- aniridia, genitourinary abnormalities such as hypospadias, cryptorchidism, partial or complete hemi-hypertrophy, macroglossia, omphalocele.
- BP hypertension.

Investigations

- 1. FBE, UEC, LFT
- 2. Urinalysis haematuria
- 3. USS of the abdomen- is the tumour intra renal? Cystic? Solid or both? Are there intravascular extensions or thrombi (inferior vena cava), tumours in the opposite kidney? Liver or abdominal metastasis? Estimate size of tumour in 3 dimensions. Helpful to scan from back to try visualise kidneys. Use large probes for large tumours.

Wilms – if more than 15 cm may obliterate affected kidneys, destructive heterogeneous mass may be cystic or a varying mixture of solid or cystic components.

If available, a Doppler study may be used to determine blood flow in the renal and inferior cava veins or seeing if the vessels are obstructed by the tumour.

- 4. CXR (PA and lateral views) detect lung metastasis.
- 5. CT scan only if available.

DDX

- 1. Neuroblastoma –generally in a poorer condition as compared to Wilms patients, severe pain, subcutaneous nodules or bilateral hematomas referred to as racoon eyes.
- 2. Burkitt's lymphoma patients are more malnourished than Wilms tumour patients, have masses elsewhere, and masses grow fast. USS may reveal one or more solid masses nearly

uniformly homogeneous. BL infiltrate kidneys resulting in homogenous enlargement in contrast to the renal destruction and renal heterogeneous tumour seen in Wilms.

Initial Staging

Group 1- Tumour limited to kidney and completely resected

Group 2- Tumour extends beyond kidney (penetration beyond pseudo-capsule, peri-aortic node involvement, renal vessel involvement beyond kidney) but completely resected.

Group 3- Residual non- haematogenous tumour confined to abdomen, e.g. tumour rupture before or during surgery, tumour not completely resectable, nodes beyond peri-aortic chain involved.

Group 4 – Haematogenous metastasis (Lungs, liver)

Group 5 – Bilateral renal involvement.

*Treatment will follow SIOP recommendations which are:

- 1. Pre- operative chemotherapy.
- 2. Surgery
- 3. Post-operative chemotherapy.

Pre-operative chemotherapy can be administered according to 2 groups.

- 1. Localised Disease consists of Group 1 in initial staging.
- 2. Metastatic Disease consists of Groups 2-5 in initial staging.

Treatment schema for Localised Disease.

Actinomycin D 45mcg/k	+			Surgery		
Vincristine 1.5mg/m ²	•	▼	*		1	
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Weeks	1	2	3	4	5	

Treatment schema for metastatic disease.



Treatment Summary

Chemotherapy (SIOP Wilm's 2001 protocol) Drugs – vincristine, actinomycin D, doxorubicin) Hydration 12 hours prior to chemotherapy with actinomycin D Allopurinol according to weight.

Localised disease (Summary)

4 week regimen Vincristine 1.5 mg/m2, maximum 2 mg Actinomycin D 45 mcg/kg IV max 2 mg

Metastatic disease

6 week regime Vincristine 1.5 mg/m2 max 2 mg Actinomycin D 45 mcg/kg IV max 2 mg Doxorubicin 50mg/m2 IV infusion

Note

*Patients with weight <12 kg and severe malnutrition should have a 2/3 reduction in dose of all drugs *VCR and actinomycin D are given IV

*Doxorubicin is given over 6 hours to avoid cardiac toxicity.

*Regimen must be altered to haematological tolerance.

*In neutropenia, give actinomycin D 3 weekly instead of 2 weekly, VCR should continue in full dose. Doxorubicin dose to 30mg/m2 in neutropenia.

*In metastatic disease CXR and USS should be done at 6 weeks to reassess 3 additional weeks of chemotherapy if sign of continued presence.

*If metastasis still present after week 9, stop curative treatment and start palliative treatment.

*Review by surgical team after Week 4 treatment for localised disease and Week 9 for metastatic disease.

Pathology

Post-operative chemotherapy is based on

- Tumour type (risk classification)
- Stage at surgery.

Table 1 Post-operative treatment strategies based on tumour type (risk classification) and pathology stage.

	Stage 1	Stage 2	Stage 3
Low risk	No further treatment	ACT-D/VCR 5 cycles	ACT-D/VCR 5 cycles
Intermediate risk	ACT-D/VCR 1 cycle	ACT-D/VCR 5 cycles	ACT-D/VCR/DOX 5 cycles
High risk	ACT-D/VCR/DOX 5 cycles	ACT-D/VCR/DOX 5 cycles	ACT-D/VCR/DOX 5 cycles

• Based on histological and surgical sub classification.

Staging (COG) Surgical

Stage 1

- Tumour limited to kidneys, completely resected.
- Renal capsule is intact
- Tumour not ruptured or biopsied prior to removal
- Vessels of the renal sinus are not involved
- No evidence of tumour present at or beyond the margins of resection.

Stage 2.

- Tumour completely resected.
- No evidence of tumour at or beyond the margins of resection
- Tumour extends beyond the kidneys a residual (penetration of renal capsule, involvement of renal sinus.)

Stage 3.

- A residual, non- haematogenous tumour is present following surgery and confined to the abdomen.
- Positive lymph nodes in the abdomen or pelvis noted
- Penetration through the peritoneal surface is observed.
- Peritoneal implants noted
- Gross or microscopic tumour remains postoperatively, including positive margins of resection.
- Tumour spillage is noted including biopsy
- Tumour is treated with pre-operative chemotherapy
- Tumour removed in more than one piece.

Stage 4

- Haematogenous metastasis (lung, bone, liver, brain) or lymph nodes beyond the abdomen or pelvis noted.

Stage 5

- Bilateral renal involvement by the tumour at diagnosis.
- Correct staging is only possible if the specimen is inked and there is a block guide.

Histological (SIOP) post 4-6 weeks of pre -op chemotherapy

Low risk

Completely necrotic

High risk

- Blastemal predominant

Intermediate

- Others not completely necrotic or blastemal predominant.

Post-operative treatment

- First dose of post-operative chemotherapy consists of vincristine alone and is given once gut peristalsis is re-established following surgery and within 21 days of the last pre- operative chemotherapy.
- The other drugs are added at week 2 of postoperative chemotherapy of surgical recovery is complete. If not consider giving a second dose of post- operative vincristine only and delay other drugs to week 3.

Post- operative chemotherapy based on pathology (if available)

Localised disease at diagnosis- post operative chemotherapy is based on tumour histology subtype and stage at surgery if available. Pathology and staging must be reliable to follow this staging. Proposed interval is 3 weeks, however if neutropenia may be extended to 4weeks. Children with metastatic disease at diagnosis but complete remission by the time of surgery should have the 3 drug 5 cycle post-operative regime.

Post-operative chemotherapy based on surgical stage.

If reliable pathological staging and risk stratification not available in time. Use surgical staging. Includes assessment of lymph nodes by the surgeon by gross inspection. A difficult operation may well mean that spillage has occurred and tumour should be upstaged. Surgical stage 1, 2(complete easy tumour resection) – 5 cycles of vincristine and actinomycin D. Surgical Stage 3 (incomplete or difficult resection or rupture/spill) – 5 cycles of vincristine, actinomycin D and doxorubicin.

Post-operative treatment Schema

1. Localised Disease at diagnosis- Stage 1, Intermediate Risk (IR)



Special Cases

Children below 6 months

Current SIOP 2001 Wilms tumour protocol recommends immediate nephrectomy for children under 6 months.

Reason being

- a relatively high proportion of non Wilms tumour(congenital mesoblastic nephroma)
- Good prognosis for Wilm's tumour at that age

- Severe chemotherapy toxicity at that age.

Cystic partially differentiated nephroblastoma

- Cystic partially differentiated nephroblastoma with very distinct features and excellent prognosis with surgery only.
- Presents in very young children < 1.5 years.
- Completely cystic renal tumour with very thin septa on USS.
- Primary nephrectomy can be considered in these children.

Bilateral tumours

- Tumour resection in one side
- Pre-operative chemotherapy to shrink tumour.
- Palliative treatment.

Relapse

- May decide to palliate.
- If only treated with 2 drugs initially, 3 cycles of 3 drugs may be considered.

Supportive treatment

- Nutrition
- Infections
- Febrile neutropenia
- Adequate pain control
- Blood transfusions

Social support

- Food and counselling on need for treatment compliance.

Side effects of chemotherapy

Actinomycin D

- Extravasation (fresh IV cannula for each administration)
- Hepatic veno-occlussive disease (VOD) liver swelling, enlargement and tenderness, thrombocytopenia, ascites and weight gain. (self-limiting but can be fatal), if suspected VOD, omit actinomycin D from next dose then re-introduce at 50% on following dose, if severe toxicity, omit actinomycin D from course.
- neutropenia

Vincristine

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Neuropathy – jaw pain, reduced or absent reflexes, foot drop and constipation

Doxorubicin

- Cardiomyopathy leading to heart failure.
- Typhlitis
- Palmer-planter erythrodysesthesia (PPE)

If actinomycin D is not available, substitute with doxorubicin for localised disease, and replace with cyclophosphamide for metastatic disease, etoposide or carboplatin using conventional doses.

Follow up

During Chemotherapy

- 1. FBE, UEC, LFT before each chemotherapy cycle
- 2. Prehydration prior to each Adctinomycin D
- 3. Prophylaxis, INAH, Septrin, Fluconazole.

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