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Treatment of Wilms tumor

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Wilms tumor also known as nephroblastoma is the most common primary malignant renal tumor of childhood. About 500 new cases are diagnosed every year in the US[1]. Over the last three decades the treatment of Wilms tumor has evolved to give >90% event free survival rates because of the collaborative efforts between surgeons, pathologists, oncologists and radiation therapists in The National Wilms Tumor Study Group now Children's Oncology Group(COG), International Society for Pediatric Oncology (SIOP) and UK Children's Cancer Study Group[2]. The SIOP and NWTSG use the same chemotherapeutic agents but the SIOP group recommends chemotherapy first, prior to surgery while the NWTSG recommends surgery followed by chemotherapy. Both approached have yielded comparable results and either system can be followed as per institutional preference[3]. Molecular studies should be done to assign the appropriate treatment strategy whenever available. In this section we will discuss the chemotherapy used for primary and relapsed Wilms tumor patients. The surgical aspects and pathology are discussed in a separate section.

Epidemiology

The incidence of Wilms tumor is approximately 8 cases per million children <15years of age with about 500 new cases in North America every year. It accounts for nearly 6% of pediatric malignancies and is the second most common malignant abdominal tumor in childhood.[1] Although peak incidence is between 2 to 5 yrs of age, Wilms tumor has also been encountered in neonates, adolescents and adults.[4]

There is a definite evidence of interracial variance with East Asian children presenting earlier than Caucasian children. In the East Asian children tumors often originate from Intra Lobar Nephrogenic Rests (ILNR); in contrast the tumors originate from the Peri Lobar Nephrogenic Rests (PLNR)in the Caucasian children. There is loss of Insulin-like Growth Factor–2 (IGF2) imprinting in patients with Peri Lobar Nephrogenic Rests (PLNR).[5]

Clinical presentation of Wilms tumor

The most common initial clinical presentation is the incidental discovery of an asymptomatic abdominal mass often by parents while bathing their child or by a physician during the course of a routine physical examination. Hypertension is detected in about 25% cases at presentation possibly due to elevated renin levels but the etiology remains unknown in majority of the cases.[6] Some patients present with abdominal pain. About 15% to 25% of cases have hematuria, usually asymptomatic. Occasionally rapid abdominal enlargement and anemia occur due to bleeding into the renal parenchyma or pelvis. In 4%- 10% of patients, Wilms tumor thrombus extends into the inferior vena cava, rarely up to the right atrium. In the presence of a thrombus obstructing the spermatic vein a varicocele may be present that persists in supine position.[7] This might be a presenting symptom that a urologist might encounter.

Table 1. Wilms Tumor Associated Syndromes

Syndrome	Features
Beckwith Wiedemann syndrome	Hemihypertrophy, macroglossia, omphalocele, visceromegaly, hepatoblastoma
Denys Drash syndrome	Pseudohermaphroditism, renal failure due to mesangial sclerosis
Pearlman syndrome	Polyhydramnios with neonatal macrosomia, nephromegaly, distinctive facial appearance, renal dysplasia, nephroblastomatosis
WAGR syndrome	Wilms tumor, aniridia, genitourinary malformations (cryptorchidism, hypospadias) and mental retardation
Frasier syndrome	Male pseudohermaphroditism, renal failure, gonadal streaks, gonadoblastoma

Microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor, or factor VII deficiency may also be part of the presentation.[6] Wilms tumor is associated with a number of syndromes that have genitourinary anomalies and can be associated with renal failure. Genitourinary anomalies including hypospadias, cryptorchidism and pseudohermaprhoditism are common presentations to the urologist. These may be a part of syndrome complex associated with Wilms tumor.[8] (Table 1)

Diagnosis and work up

An abdominal mass in a child should be considered malignant until proven otherwise. Imaging studies including KUB abdomen, abdominal US, CT and/or MRI of the abdomen should be the first step to define the origin of the mass. Other malignant abdominal masses in this age group include neuroblastoma arising from the adrenal gland, rhabdomyosarcoma arising in the retroperitoneal musculature, germ cell tumor arising from the ovary and lymphoma. Clear cell sarcoma and malignant rhabdoid tumor of the kidney are rare. Ultrasound with doppler of renal veins and inferior vena cava is a useful first study that can not only look for Wilms tumor, but also evaluate collecting system of the kidneys and thrombi in the renal veins and/or inferior vena cava. Abdominal CT or MRI are useful to define the extent of the disease prior to surgery and will assess integrity of the contralateral kidney. In bilateral cases, MRI may be a better guide for a nephron sparing surgery.[9] If histological diagnosis confirms clear cell sarcoma of the kidney, a bone scan is indicated. A brain MRI is indicated in case of rhabdoid tumor of the kidney to look for metastasis. Chest CT is more sensitive than chest X-ray to detect pulmonary metastasis for baseline and follow up studies.[10]

Once the mass is confirmed to be of renal origin and extent of disease noted; the patient may undergo nephrectomy and confirmation of pathology. A biopsy is generally done only if the mass is considered unresectable.

Pathology

Pathology is important for risk stratification and is discussed in detail in a separate chapter. Based on presence or absence of anaplasia, Wilms tumor is classified as favorable or unfavorable histology. Anaplastic histology is classified as focal or diffuse with focal anaplasia having a better prognosis. Loss of heterozygosity at 1p and 16q are important for risk stratification.

Staging

Staging is based on extent of tumor outside the kidney parenchyma and abdomen. This staging is also applicable for rhabdoid tumor of the kidney and clear cell sarcoma of the kidney. In the NWTSG system any tumor that is considered inoperable or receives preoperative chemotherapy, automatically gets classified as stage III. Any tumor that gets biopsied, (fine needle or trucut or open) prior to removal is considered stage III.

Risk stratification

Risk stratification is an important step to decide the exact chemotherapeutic regimen.

COG currently stratifies favorable histology tumors into very low, low, standard and higher risk groups.

Treatment – Historical perspective

Treatment is multimodal and involves surgery, chemotherapy and radiation. There are two different approaches to treatment. The Americans (COG) recommend upfront surgery while the Europeans (SIOP and UKCCSG) recommend chemotherapy prior to surgery. Since preoperative chemotherapy alters tumor histology, tumor might be assigned lower risk group. Although surgery at presentation gives an accurate diagnosis there is an increased risk of tumor rupture and spillage during surgery. Adequate imaging studies should be done prior to surgery. Both approaches have yielded excellent and similar overall survival rates.

Treatment of Wilms tumor has evolved over the last three decades with event free survival greater than 90%. Now the focus is on reducing the exposure to chemotherapy and radiation to reduce potential long term adverse effects.

Dactinomycin (Actinomycin-D) was the first drug shown to have activity in Wilms tumor by Farber *et al*.[11] Subsequently vincristine, doxorubicin and cyclophosphamide were shown to have activity against Wilms tumor.

In 1969 the National Wilms Tumor Study Group was established to determine the different therapeutic agents and the efficacy of chemotherapy for Wilms tumor.[8]

Favorable histology Wilms tumor

The NWTSG 1 demonstrated that the combination of vincristine and dactinomycin was more effective than either drug alone.[12]

NWTSG 2 demonstrated that 6 months of therapy with vincristine and dactinomycin was as effective as 15months of therapy for children with group I disease. It also demonstrated that addition of doxorubicin to the combination of vincristine and dactinomycin improved relapse free survival in stage II and III Wilms tumor.[13]

NWTSG 3 demonstrated that patients with stage I favorable histology can be treated successfully with 11 week regimen composed of vincristine and dactinomycin without abdominal radiation. It was also shown that stage II favorable histology patients could be treated with dactinomycin and vincristine without exposing the patient to radiation and doxorubicin. On the other hand children with stage III Wilms benefited from addition of doxorubicin with a lower dose of radiation. In the stage IV patients, addition of cyclophosphamide to a three drug regimen did not show additional significant benefit.[14]

NWTSG 4 established that the pulse intense regimens had less toxicity than the long term regimens. This reduced the duration of chemotherapy from 15 months to 6 months for stage II to IV Wilms tumor.[15]

The NWTSG 5 established the role of LOH at 1p and 16q as a poor prognostic marker for relapse in favorable histology Wilms. It also showed that for children less than two years of age with tumor weight less than 550 gram but not greater than 550 gram could be successfully observed after surgery without chemotherapy.[16,17]

Current treatment

Treatment guidelines summarized here are as per the latest COG protocols AREN 0532 for very low risk and low risk tumors, AREN 0533 for high risk favorable histology tumors and AREN 0321 for high risk renal tumor. Table 4 details chemotherapy sequence for regimens EE4A, DD4A and M. Drug doses vary by age and treatment regimen. Please consult individual regimen for drug doses.

Table 5 outlines the risk group and treatment regimen to follow. LOH when present should be present and both 1p and 16q. Stage IV patients with pulmonary metastases are treated with DD4A and re-evaluate for lung metastasis at 6 weeks after treatment. If no lung metastasis detected at 6 weeks then no need for radiation.

High risk - Stage III and Stage IV with LOH at 1p and 16q treat with regimen M which is a 5 drug regimen with cyclophosphamide and etoposide in addition to the 3 drug combination of doxorubicin, dactinomycin and vincristine over 33 weeks.

Complications during treatment

Chemotherapy is associated with short, intermediate and long term complications and patients should be advised and monitored for adverse effects. Most of the Wilms tumor chemotherapy is given on an outpatient basis in the United States.

Adverse events: Guidelines when to modify treatment

1. Vincristine should not be started until peristalsis and enteral nutrition is established after surgery. SIADH with seizures, paralytic ileus and neuropathy causing diplopia rarely vocal cord paralysis can occur. These require omission of one or two doses of vincristine and restarting a lower dose with subsequent increments as tolerated.

2. In case of typhlitis or febrile neutropenia chemotherapy is withheld until complete resolution of the condition.

3. Greater than 10% reduction of Ejection fraction is an indication to delay doxorubicin. After week repeat cardiac studies and doxorubicin resumed if study results are normal.

4. Dactinomycin and doxorubicin modify tissue response to radiation therapy. Onset of tachypnea following administration of these drugs after whole lung irradiation can represent radiation

pnuemonitis. 50% dose reduction is done for both the drugs for 6 weeks after lung radiation or drugs are administered concurrently with radiation.

5. Sinusoidal obstruction syndrome (SOS) previously known as veno- occlusive disease of the liver is suspected when the patient presents with right upper quadrant abdominal pain, elevated bilirubin and unexplained weight gain more than 10%. Liver dysfunction related to SOS requires vincristine, actinomycin D and doxorubicin dose modification and is usually based upon bilirubin levels as written in individual protocol for each of these drugs.

6. Vincristine should be continued irrespective of myelosuppression but other drugs are usually withheld until absolute neutrophil count becomes greater than 750 and platelet count becomes greater than 75,000.

7. Hold dose of cyclophosphamide for gross hematuria and use MESNA in the future.

8. Mucositis that interferes with oral intake may warrant 25% reduction in the dose of doxorubicin, actinomycin D or etoposide during subsequent cycles.

Radiation Therapy

Wilms tumor is a very radiosensitive tumor. With the advent of effective chemotherapy current indications and doses of radiation are modest in an effort to reduce long term effects.

Patients with Stage I and Stage II favorable histology do not need abdominal irradiation. Patients with Stage III favorable histology Wilms tumor receive radiation to the flank. In patients without LOH whose pulmonary nodules resolve on CT scan at 6 week of DD4A need not receive radiation to the lungs. Patients who have persistence of lung nodules at 6 weeks after treatment on DD4A, or who have LOH, whole lung radiation is recommended. Higher doses of irradiation may be indicated for other sites or metastases like the liver, bone brain and lymph nodes. Table 7 outlines the indications and doses for irradiation in case of metastasis.

Treatment of Unfavorable Histology Wilms tumor

Anaplasic histology Wilms tumor accounts for 7.5% of Wilms tumor and accounts for a disproportionately large number of relapses and deaths among children with renal tumors.

The NWTSG 3 and 4 demonstrated that addition of cyclophosphamide to the three drug regimen of dactinomycin, vincristine and doxorubicin improved relapse free survival when treated for 15 months.[19] The NWTSG 5 study also showed that for stage II to IV anaplastic histology Wilms tumor cyclophosphamide and etoposide alternating with the three drug regimen of dactinomycin, vincristine and doxorubicin had improved relapse free survival. The NWTSG 5 study also showed that the stage I anaplastic histology Wilms had lower event free survival as compared to historical controls after the two drug regimen with dactinomycin and vincristine.[20]

Here we will outline the treatment overview for unfavorable histology Wilms tumor. Current treatment guidelines as per AREN 0321 recommend DD4A for stage I to III focal anaplastic tumors and stage I diffuse anaplastic histology. The UH1 and UH2 regimens for higher stage anaplastic histology encountered unacceptable toxicities on the study and doses were modified and accrual suspended in these protocols. Treatment for these high risk tumors remains a challenge and consultation by a center experienced in treatment of high risk situations is recommended.

Treatment of relapsed disease

Patients who were less than 24months of age and received surgery only and no chemotherapy will be stages according to tumor extent at relapse. Patients with complete resection will receive treatment with two drugs for 18 weeks (Regimen EE4A). Patient with lymphatic or hematogenous spread will receive 3 drug combination with Doxorubicin, vincristine and dactinomycin (Regimen DD4A) for 24 weeks and radiation to the site of relapse.[18]

Patients who received 2 drug combination as initial treatment now receive upfront surgery followed by 4 drug combination including doxorubicin, vincristine, cyclophosphamide and etoposide over 24 weeks (Regimen I in NWTSG V). Patients who received doxorubicin in their initial treatment plan will now receive a 4 drug

combination of cyclophosphamide and etoposide with carboplatin and etoposide followed by surgery at week 13. After surgery they will receive radiation along with this 4 drug combination as consolidation and maintenance phases. Other drugs including combinations with gemcitabine and docetaxel, irinotecan and temozolomide have activity against Wilms tumor.

Table 2. Wilms Tumor Staging (COG)

Stage	Criteria after Surgery
Stage I	Tumor limited to the kidney and completely resected. Renal capsule intact. Tumor not ruptured or biopsied before removal. Vessels of renal sinus not involved. No evidence of tumor beyond surgical margins.
Stage II	Tumor completely resected but originally extended beyond the kidney, as evidenced by one of the following
	Penetration of renal capsule, invasion of renal sinus vessels or soft tissue
Stage III	There is residual nonhematogenous tumor present following surgery that is confined to the abdomen. Any of the following may have occurred
	Lymph node involvement within the abdomen, tumor has penetrated through the peritoneal surface, tumor implants on the peritoneal surface, gross or microscopic tumor residual, preoperative chemotherapy regardless of biopsy, tumor spillage during surgery, extension of tumor within the vena cava abdominal or thoracic including extension up to the heart.
	Tumors that are considered inoperable should be treated as stage III
Stage IV	Hematogenous metastases (*e.g*. lung liver bone brain)
	Lymph node metastases outside the abdominopelvic region.
Stage V	Bilateral involvement at diagnosis. Each side should be staged separately.

Future directions

Although most children with Wilms tumor have excellent outcomes, relapse is a problem in some. There is room for improvement. Treatment of unfavorable histology remains a challenge. Molecular biology is currently being explored. In the future genome profiling may help predict tumor response to therapeutic modalities. Therapeutic agents useful in other malignancies may be active in relapsed Wilms.

Table 3. Risk Stratification and Treatment Assignment (COG guidelines 2009)

Age	Tumor weight	Stage	LOH	Rapid response	Risk group
<2yrs	<550 g	I	Any	-	Very low
Any	>550g	I	None	-	Low
>2yrs	Any	I	None	-	Low
Any	Any	II	None	-	Low
>2yrs	Any	I	LOH*	-	Standard
Any	>550g	I	LOH*	-	Standard
Any	Any	II	LOH*	-	Standard
Any	Any	III	None	Any	Standard
Any	Any	III	LOH*	Any	Higher
Any	Any	IV	LOH*	Any	Higher
Any	Any	IV	None	Yes	Standard
Any	Any	IV	None	No	Higher

**LOH – Loss of Heterozygosity for both 1p and 16q*

Table 6. Adverse Effects of Chemotherapy

Drug	Known adverse effects
Vincristine	Jaw pain, constipation, paresthesias, peripheral neuropathy leading to foot drop
Actinomycin – D	Nausea*, myelosuppression, Venoocclusive disease(VOD) of the liver also known as Sinusoidal obstruction syndrome (SOS), Dactinomcin radiation recall
Doxorubicin	Nausea*, mucositis, mouth sores, pink or red color to urine or sweat, cardiotoxicity, myelosuppression, cardiotoxicity rare with current dose recommendations
Cyclophosphamide	Nausea*, hemorrhagic cystits, immune suppression, gonadal dysfunction, secondary leukemia(rare)
Carboplatin	Nausea*, myelosuppression, ototoxicity(rare)
Etoposide	Nausea*, myelosuppression, secondary leukemia(rare)

Table 7. Radiation therapy guideline (COG 2009)

Tumor Characteristics	Radiation Dose/Field
Stage I and II favorable histology	None
Stage III favorable histology Stage III local tumor spillage, flank or peritoneal biopsy, open biopsy	10.8Gy flank
Stage III with preoperative tumor rupture or cytology positive ascites or diffuse operative tumor spillage or peritoneal seeding	10.5Gy whole abdominal irradiation
Unresectable peritoneal implants	21Gy whole abdominal irradiation
Lung metastases*	Whole lung irradiation Age<12mo 10.5Gy Age>12mo 12Gy
Anaplastic histology Focal anapalsia Stage I to III Diffuse anaplasia Stage I to II	10.8Gy flank
Diffuse anaplasia Stage III	19.8Gy flank
Unresectabel liver metastases	19.8Gy liver

** Only for lung metastases that do not resolve at 6 weeks on DD4A for patients without LOH and all lung metastases with LOH*

Table 5. Treatment Guidelines

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