Comparative study on the effect of preoperative chemotherapy on downtaging and surgical outcome in pediatric Wilm's tumor

Thesis

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ABSTACT

Wilm's tumor is the most common malignant renal tumor in children represents 6% of childhood cancers. WT presented by abdominal mass, loss of weight, anemia, hypertension. Aim of the work is to compare the effect of preoperative chemotherapy versus the standard up front surgical resection. Results of this study revealed that in group I: Resectability of the tumor in 19 child versus one child is highly significant. Down staging in group I is highly significant

key Words:

Pediatric cancer- wilm's tumer- nephroblastoma – SIOP

Management

Diagnosis

Clinical presentation

The average age at presentation for Wilms' tumor (WT) is 3 years. Wilms' tumor is relatively uncommon in the first 3 months of life; however, one third of all cases are seen between 6 and 12 months of age. Although Wilms' tumor is rare after 8 years of age, it may still occur in older children, adolescents, and occasionally young adults ***(Tongaonkar et al., 2007).***

There are no specific clinical features of WT. Most commonly patients present with a palpable abdominal mass accidentally noted by the parents or in the course of a routine clinical examination. However, about one-third of patients present with abdominal pain, anorexia, vomiting, malaise or a combination of these symptoms. Gross or microscopic hematuria is found in 30% of patients. In rare cases of renal vein or caval extension of tumor, varicocele, hepatomegaly, ascites or congestive heart failure may be present. Hypertension is present in about 25% and is attributed to increase in renin activity. Occasional presentation in a subset of patients is rapid enlargement of the abdomen associated with fever, anemia and hypertension as a result of sudden subcapsular hemorrhage***(Tongaonkar et al., 2007).***

Acquired von Willebrand's disease may occur in less than 10% of patients. Features of congenital syndromes associated with WT like genitourinary malformation (hypospadias, cryptorchidism etc), aniridia, BWS-associated facial dysmorphism, hemihypertrophy etc may be present in 13-28% of patients ***(kalapurakal et al .,2004).***

Imaging studies

The imaging studies for WT are designed to establish the following:

1. Nature of the mass.
2. Organ of origin .
3. Presence of functioning contralateral renal tissue.
4. Presence of bialateral disease.
5. Patency of IVC and renal vein.
6. Presence of distant metastases ***(Ritchey ,2002).***

Abdominal ultrasound is performed and can confirm that the kidney is the site of the tumor, determines whether the mass is a cystic or solid tumor and indicates if the tumor extends into the veins exiting the kidney and going back to the heart, renal vein, inferior vena cava (IVC), or right atrium ***(Ehrich , 2007).***

Advances in radiological techniques are able to detect non-palpable Wilms' tumors, nephroblastomatosis, and tumor spread much earlier and in a less invasive manner than in the past. An abdominal ultrasound study of the mass and color-duplex investigation of the renal vessels should be performed. Thus, the extent of renal involvement (contralateral kidney), the renal vein, the inferior vena cava (IVC) and the liver can be assessed. Additionally, high-resolution sonography may detect areas of nephroblastomatosis usually presenting as multiple solid, subcapsular, hypovascular and hypoechogenic nodules or cysts ***(Gupta et al., 2005).***

CT scans of the chest and the abdomen should also be done as baseline diagnostic procedures for complete evaluation of the extent of the mass. Following the NWTS-5 recommendations, positive findings seen in chest CT but not on chest radiograph should be ignored. Whether the accuracy of CT or

Management

MRI obviates the need for surgical exploration of the contralateral kidney remains controversial. MRI studies have a predominant role in demonstrating the relation of the tumor to other organs. MRI, along with ultrasound is more sensitive than CT for assessing extension of a tumor thrombus into the inferior vena cava (IVC) with the additional possibility of MR-venography. Nephrogenic rests (NRs) as small as 4mm typically appear as homogeneous lesions after Gadolinium enhancement, different from the heterogeneous appearance of Wilms' tumor. SIOP-investigators strongly recommend a judgement by a reference radiologist because in these studies preoperative chemotherapy without histopathological diagnosis is favored ***(Gupta et al., 2005).***

In contrast, a neuroblastoma (another childhood tumor that may sometimes be confused with Wilms' tumor on CT scan) rarely affects the urine collecting system and generally indents or pushes on the kidney tissue rather than being surrounded by it. Neuroblastoma pushes the kidney downward (if it arises from the adrenal gland) or to the side (if it arises from celiac ganglia).

CT scan also defines the Wilms' tumor as being within the kidney; identifies the presence of enlarged and suspicious lymph nodes; evaluates the possible presence of a second Wilms' tumor in the opposite kidney; assesses involvement of the tumor into the veins leaving the kidney and going back to the heart (renal vein, inferior vena cava, right atrium), and determines if the patient has spread of tumor to the liver ***(Cohen, 1996)***.

Magnetic resonance imaging (MRI) may be of help in patients with suspected inferior vena cava or right atrial tumor or in patients with bilateral Wilms' tumor.

Recent reports have indicated that MRI can help to distinguish between nephrogenic rests and wilms'tumor ***(kalapurakal et al .,2004).***

Positron emission tomography (PET) scanning is a new modality to cancer imaging. It appears to be useful in some malignancies which helps distinguish normal and malignant tissue. In WT their have been a few case reports, but its role has been not yet defined ***(Ehrich, 2007)***

Screening does increase the proportion of children in whom the tumor can be removed while keeping part of the kidney. Current recommendations are for ultrasound every 3 months until 6 to 8 years of age. For children with Beckwith-Wiedemann syndrome and hemihypertrophy, the adrenal glands and liver should be evaluated in addition to the kidney because this group is also at risk for liver tumors (hepatoblastoma) and neuroblastoma ***(Ebb et al .,2005).***

Treatment

Treatment strategies differ between the US, favoring immediate nephrectomy, and Europe, favoring preoperative chemotherapy. The UK treatment strategy also differs slightly from European strategies, favoring pre nephrectomy chemotherapy only after initial tumor biopsy to exclude the small percentage of children who have benign pathology or non-Wilms' tumors, which require different treatment modalities. These approaches have the definitive advantages of a decrease in intraoperative tumor rupture and down-staging for the European approach, and definitive histologic diagnosis and chemotherapy-naive tumor for the US approach. The UK strategy reaps the benefits of histologic diagnosis as well as preoperative chemotherapy prior to nephrectomy. The usual approach in most patients is nephrectomy followed by chemotherapy with or without postoperative radiotherapy ***(Metzger et al ., 2005).***

Chemotherapy

Three highly effective drugs are used in the first-line therapy of Wilms' tumors: dactinomycin, vincristine, and doxorubicin. Four other drugs are used in patients who experience relapse or do not respond to the combination of dactinomycin, vincristine, and doxorubicin. These include cyclophosphamide, ifosfamide, carboplatin, and etoposide.

The best combination of agents and duration of therapy has been developed by several cooperative clinical-trial groups worldwide, including Societe Internationale d'Oncologie Pediatrique (SIOP), UK Children's Cancer Study Group (UKCCSG), German Pediatric Oncology (GPO) group, and National Wilm's Tumor Study Group (NWTSG). Through successive clinical trials these groups have continued to refine therapy and decrease the acute and long-term morbidity associated with the treatment of Wilms' tumor ***(kalapurakal et al., 2004).***

1-Neoadjuvant chemotherapy indications include:

Bilateral Wilms' tumor

Inoperable tumor

Intravascular extension into IVC above hepatic veins Tumor in solitary kidney

2. Adjuvant chemotherapy

Regimen EE4A • 18 week course Actinomycin D and Vincristine Stage I/II FH WT Stage I focal or diffuse anaplasia WT

Regimen DD4A • 24 week course Actinomycin D, Vincristine, Doxorubicin Stage III/IV FH WT Stage II - IV Focal anaplasia

Regimen I • 24 week course Vincristine, Doxorubicin, Cyclophosphamide, Etoposide Stage II - IV diffuse anaplasia ***(Gupta et al., 2005)***.

SIOP studies

In the SIOP studies, the therapeutic approach has been focused on developing stage-specific strategies after prenephrectomy therapy. Stage classification and histo-pathological diagnosis are delayed until surgery, which occurs several weeks after clinical and imaging diagnosis. The use of prenephrectomy therapy facilitates surgery in most tumors, because they shrink after the administration of radiotherapy or chemotherapy. This approach reduces the incidence of peri-operative tumor rupture. In addition, chemotherapy-induced tumor shrinkage results in a different stage distribution of patients who undergo immediate nephrectomy to that of patients who receive prenephrectomy chemotherapy by the NWTSG surgical pathological staging system ***(Weirich et al., 2001).***

Finally, this approach establishes in vivo the efficacy of the chemotherapeutic agents used, allowing consideration of other chemotherapeutic agents after surgery for patients whose tumors did not show signs of response. A drawback of administering prenephrectomy chemotherapy is that treatment is initiated without histopathological tissue confirmation ***(Bocon et al.,2000).***

The first and second SIOP trials showed that preoperative irradiation reduces the incidence of tumor rupture and recurrence-free survival but not overall survival.

SIOP-5 showed that preoperative chemotherapy with vincristine and dactinomycin is as effective as preoperative irradiation plus dactinomycin in preventing tumor rupture. SIOP-6 showed that there was no difference in survival when children with SIOP stage I disease were randomly assigned either 17 weeks or 38 weeks of postoperative chemotherapy with vincristine and dactinomycin ***(Lemerle et al .,1993)***.

In SIOP-9, the main objective was to find the optimum duration of preoperative chemotherapy (4 weeks or 8 weeks), to increase further the rate of SIOP stage I tumors and reduce the number of SIOP stage II and III tumors requiring more

aggressive therapy. No advantage was noted for 8 weeks of therapy ***(Tournade et al ., 2001).***

In SIOP-93-01, postoperative therapy was based on stage and pathological response to chemotherapy. From postoperative histology, tumors were classified as low, intermediate, or high risk according to the Stockholm working classification of renal tumors ***(Kalapurakal et al .,2004).***

UKCCSG

Like the NWTSG, the UKCCSG initially used postoperative treatment regimens stratified by stage and histology after primary nephrectomy. Their first study (UKW1) showed that vincristine alone for 6 months was as effective as vincristine and dactinomycin for patients with stage I favourable-histology Wilms' tumor. The results for stage III favourable-histology patients were similar to those reported by NWTSG investigators, but the 6-year survival for stage IV patients with lung metastases (65%) was significantly worse than the 4-year survival (82%) reported by the NWTSG." This discrepancy was attributed to the routine inclusion of lung irradiation in all lung stage IV patients on NWTSG treatments ***(Pritchard et al .,1995).***

In UKW2, patients with stage I favourable-histology Wilms' tumor treated with ten weekly doses of vincristine had similar outcome (95% 4-year survival rate) to that noted for comparable patients registered on the NWTSG trials. However, more careful analysis suggested that the excellent outcome in stage I favourable-histology Wilms' tumor does not apply for children aged four years or older ***(Pritchard et al .,2003).***

For these children, the UKCCSG does not recommend a 10-week course of postoperative vincristine monotherapy. Finally, although better than that reported

for UKW1, the 4-year overall survival for stage IV patients in UKW2 (75%) remained inferior to that reported by the NWTSG ***(Mitchell et al., 2000).***

NWTSG

The first three NWTSG trials showed that postoperative abdominal radiotherapy was unnecessary for patients with stage Iand II after nephrectomy. The addition of doxorubicin to the combination chemotherapy decreased the risk of relapse but did not improve overall survival for children with stage III favourable-histology Wilms' tumor. Moreover, the dose of abdominal irradiation could be decreased to 10-8 Gy for stage III favourable-histology patients receiving the three-drug regimen. The addition of cyclophosphamide to the combination of vincristine, dactinomycin, and doxorubicin did not improve the outcome for patients with stage IV favourable-histology Wilms' tumor, but it did improve relapse-free and overall survival in patients with stage II to IV anaplastic-histology Wilms' tumor (***D'Angio et al .,1989)***.

The fourth NWTSG study investigated the efficacy, toxicity, and cost of different schedules of dactinomycin and doxorubicin administration, finding that dactinomycin could be given safely in 1 day rather than over 5 days and doxorubicin in 1 day rather than over 3 days. These so-called pulse-intensive regimens were as effective as the standard courses but were accompanied by less severe toxicity and fewer health-care encounters .As a consequence pulse-intensive becomes the standard of care for treatment of Wilms' tumor***(Green et al., 1998).***.

The major aim of the non-randomised NWTS-5 trial therefore was to assess the prognostic value of loss of heterozygosity(LOH) at chromosomes Ip and

16q. Results from NWTS-5 are LOH is associated with favorable histology and worse outcome for stage I ***(Kalapurakal et al ., 2004).***

Synchronous bilateral Wilms' tumor

About 6% of all children with Wilms' tumor present with simultaneous bilateral tumors (stage V) at the time of diagnosis. Although more than 70% survive, these children are at high risk of renal failure. This risk has led to the recommendation that such patients undergo bilateral renal biopsy with staging of each kidney followed by chemotherapy to shrink the tumor and facilitate renal-sparing procedures. Primary excision of the tumor masses is not recommended.

After 6-8 weeks of chemotherapy, the patient is reassessed and the feasibility of resection assessed. A second-look procedure may be indicated. Additional chemotherapy or radiotherapy may be needed, but surgery should not be delayed indefinitely. In general, definitive surgery should be done within 12-16 weeks of diagnosis to limit the risk chemoresistant clonal expansion ***(Ritchey et al .,1996)***.

Radiotherapy

Treatment with radiation continues to have an important role in the management of Wilms' tumor. The past decade has witnessed remarkable technical innovations in radiation delivery systems and treatment planning software. The use of three-dimensional treatment planning systems based on CT and MRI will enable accurate tumor targeting and superior protection of adjacent normal structures. This technology could be used to deliver conformal radiotherapy for abdominal tumor recurrences and for metastatic sites in the brain, lung, and liver ***(Kalapurakal et al ., 2004)***.

Flank/abdominal irradiation

Successive NWTSG trials have refined the indications for radiotherapy. The first study of Wilms' tumor showed that radiotherapy conferred no advantage in children younger than 24 months with stage I tumors who also received 15 months of dactinornycin. That study also showed that in stage III tumors, with local tumor spill or previous biopsy, there was no need for irradiation of the whole abdomen, thus sparing them the toxicity associated with such irradiation ***(D'Angio et al ., 1978)***.

NWTS-2 showed that radiotherapy could be avoided in all children with stage I Wilms' tumor ***(Thomas et al., 1984).***

In NWTS-1 and NWTS-2, an age-adjusted dose schedule was used for flank irradiation: 18-24 Gy for children younger than 8 months; 24-30 Gy for those aged 19-30 months; 30-35 Gy for those aged 31-40 months; and 35-40 Gy for children older than 40 months. The abdominal relapse rate was 3-5% in stage II and III tumors, and there was no dose-response relation across these dose ranges. The third NWTSG study proved that radiotherapy could be avoided in children with stage II tumors if vincristine and dactinomycin were given. This study also showed that children with stage III favourable-histology tumors who received 10-8 Gy radiotherapy and vincristine, dactinomycin, and doxorubicin had similar tumor control to those who received 20 Gy with vincristine and dactinomycin. This was an important finding because it eliminated the need for an age-adjusted dose schedule and significantly reduced the recommended dose of radiation ***(Thomas et al., 1991).***

In NWTS-2, the predisposing factors for local tumor recurrence were histology, delay of 10 days or longer before starting radiotherapy, and small radiation -field size ***(Thomas et al., 1984).***

NWTSG investigators showed that a delay of 10 days or longer did not significantly influence flank or abdominal tumor recurrences among children with favourable-histology tumors treated on NWTS-3 and NWTS-4 ***(Kalapurakal et al., 2004).***

However, owing to the rather narrow range of 8-12 days after nephrectomy by which time radiotherapy was administered, the possibility of detecting a meaningful difference in recurrence was limited. Children with abdominal tumor relapse had a poor prognosis , in NWTS-3, 87% of children with a local tumor recurrence died of the disease ***(Garaventa et al., 1994).***

In NWTS-4, the frequency of abdominal tumor recurrence in children with local tumor spill and stage II tumors of all histologies was 16.5%. These children did not receive flank irradiation according to the revised guidelines in NWTS-4. Survival after local recurrence was poor, with only 43% surviving at 2 years. The incidence of tumor recurrence for patients with stage III tumors with local spill after irradiation was only 7.8% ***(Shamberger et al., 1999).***

Although diffuse anaplastic tumors are resistant to chemotherapy, and presumably radiotherapy, these tumors have not shown a radiation dose response between 10-8 Gy and 40 Gy. The optimum radiation dose for anaplastic Wilms' tumor remains unknown**.**

The current standard of care includes flank/abdominal irradiation (10.8 Gy in six fractions) for stage III favourable histology tumors and stage II-III diffuse anaplastic Wilms' tumors ***(Green et al., 1994)***.

The role of radiation therapy in patients with Wilms’ tumor has changed over the years. Because of the frequency of late side effects (i.e., heart failure, lung