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Synchronous bilateral Wilms tumor with complete radiographic response managed without surgical resection: A Report from the National Wilms Tumor Study-4

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Abstract

Purpose—We reviewed the long-term local tumor control in patients with bilateral Wilms tumor (BWT) who received no definitive surgical therapy to one kidney after complete radiographic resolution after initial chemotherapy.

Methods—National Wilms Tumor Study-4 (NWTs-4) enrolled 3,335 patients (pts) during the period August 1986 through August 1994. There were 188 pts with BWT or 5.6% of the total enrolled. The treatment records and imaging reports were reviewed to ascertain those children who had documented tumors without definitive surgical therapy after initial treatment. Patients who did not have renal surgery due to progression of tumor were excluded from this study.

Results—Eleven children had no definitive surgical treatment for renal lesions in one kidney (right - 6, left -5) after initial treatment with chemotherapy and or radiation therapy. The pretreatment size of the lesions were <3cm (4pts), 3–6 cm (5pts), >6cm (1pt) and unknown (1 pt). Prechemotherapy biopsy was performed in 6 of 11 patients. Lesions <3cm (1pt), 3–6cm (3pt), >6cm (1pt) 1 unknown. Four biopsies showed favorable Wilms histology. One lesion (4cm) showed an intralobar

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nephrogenic rest, another lesion of unknown size was read as favorable histology vs. perilobar nephrogenic rest. Five lesions were not biopsied. (4pts <1 cm, 1 pt = 3cm.)

Only two children in this study received radiation treatment. One child received 1050 cGy whole abdominal radiation and one child received 1060 cGy to the left flank post nephrectomy. Radiation therapy was not given to any patient due to failure of the tumor to respond to chemotherapy.

Five patients received treatment regimen EE-4A, dactinomycin and vincristine. The duration of therapy ranged from 24 –102 weeks for an average of 55.6 weeks. Three patients received treatment regimen DD-4A, dactinomycin, vincristine and doxorubicin for 28, 52 and 52 weeks respectively. Three patients received two separate regimens of chemotherapy. One child was treated with dactinomycin, vincristine and cyclophosphamide for 60 weeks and then received regimen EE-4A for 24 weeks. Another patient received regimen EE-4A for 16 weeks and then regimen DD-4A for 36 weeks. One child received regimen EE-4A for 12 weeks and then regimen DD-4A for 40 weeks. Management of the contralateral kidney was complete nephrectomy in all eleven patients. There were no local relapses in the renal tumor bed. All patients were alive at a median follow-up of 9 years (range 9 mo–15 yrs).

Conclusion—Children with synchronous BWT or Wilms tumor and contralateral nephrogenic rests that have radiographic resolution, after initial treatment have a low risk for local relapse. These children should be followed by serial imaging.

Keywords

Wilms-Bilateral

Introduction

The National Wilms Tumor Study Group (NWTSG) has completed five protocols of multimodal management of children with Wilms tumor. The recognition of prognostic factors including tumor stage, histology and cytogenetics has produced highly effective treatment regimens with the most intensive regimens reserved for patients with aggressive unfavorable disease. The absence of a defined protocol for the management of children with bilateral Wilms tumors (Stage V disease) has led to great variability in the treatment of these often complex patients. The NWTSG had recommended that all children with bilateral lesions receive chemotherapy prior to surgical resection in an effort to preserve renal parenchyma. Many tumors are documented by imaging studies to have a dramatic response to chemotherapy. The management after initial chemotherapy in bilateral Wilms tumor (BWT) patients has been controversial. The NWTSG has included children with bilateral Wilms tumors and those with unilateral Wilms and contralateral renal nodules that ultimately were identified as nephrogenic rests as stage V. This report describes the treatment of children with synchronous bilateral renal lesions enrolled in NWTSG-4 with tumors managed by chemotherapy and no definitive surgical therapy after complete radiographic response.

Methods

Of the 3,335 patients enrolled in NWTSG-4 (August 1986 through August 1994), there were 188 pts with BWT or 5.6% of the total enrolled. The authors (MR, RCS, TH) reviewed the charts including treatment records, operative reports, and imaging reports of these children. This review identified 11 children who did not have surgical resection of the primary tumor in one kidney after initial treatment with chemotherapy. Patients that did not have renal surgery due to progression of tumor were excluded from this study as were those without adequate radiographic follow-up.

Results

The radiographic response of the tumors that did not undergo removal after chemotherapy was documented by CT scan. In 11 children; there was complete resolution of the renal mass. The pre-treatment size of these lesions was <3cm (4pts), 3–6 cm (5pts), >6cm (1pt) and unknown (1 pt). Initial biopsy of the resolving lesion was performed in 6 of 11 patients. Of the lesions biopsied four were favorable histology Wilms tumor, one was an intralobar nephrogenic rest, and one read as favorable histology Wilms tumor vs. perilobar nephrogenic rest. In both patients with nephrogenic rests the contralateral nephrectomy specimen demonstrated favorable histology Wilms tumor.

Management of the contralateral kidney was complete nephrectomy in all eleven patients. Local relapse in the renal tumor bed did not occur. Two patients received radiation treatment. One patient received 1050 cGy to the whole abdomen and one 1060 cGy to flank post nephrectomy. Radiation therapy was not given to any patient due to failure of the tumor to respond to chemotherapy. Five patients received treatment regimen EE-4A, dactinomycin and vincristine. The duration of therapy ranged from 24–102 weeks for an average of 55.6 weeks. Three patients received treatment regimen DD-4A, dactinomycin, vincristine and doxorubicin for 28, 52 & 52 weeks respectively. Three patients received two separate regimens of chemotherapy. One patient received dactinomycin, vincristine and cyclophosphamide for 60 weeks and EE-4A 24 weeks, one received EE-4A for 16 weeks and DD-4A for 36 weeks. One child received 12 weeks of EE-4A and 40 weeks of DD-4A. The reasons for an additional regimen of chemotherapy included: chemoresistance, unfavorable histology and the reason for the change in chemotherapy in the final patient was unclear. All patients are alive at a median follow-up of 9 years (range 15yr-9mo).

Discussion

Children with bilateral lesions represent 5% of all patients with Wilms tumor. The incidence reported to the NWTSG has remained stable since the report by D'Angio et al in 1976. (1) NWTSG has recommended preoperative chemotherapy for children with BWT for the past twenty years to maximize the possible preservation of renal parenchyma. (2)[Bishop] Review of NWTSG patients has found a higher incidence of renal failure in patients with BWT (9% synchronous, 18 % metachronous) versus 1% incidence of renal failure in unilateral Wilms patients. The primary cause of renal failure was bilateral nephrectomy (74%) for persistent or recurrent tumor. The second leading cause for renal failure was treatment related factors such as radiation, chemotherapy or surgical complications. (3) (Ritchey)

While the focus has been on renal preservation, survival is the most important endpoint in treating children with cancer. Recent data suggest that survival is lower for patients with BWT than unilateral Wilms tumor. (4) [Dome] It is difficult to know if the approach of preoperative chemotherapy to preserve renal parenchyma has an impact on outcome compared to primary surgical resection for BWT. There has never been a prospective randomized study performed by either the NWTSG or International Society of Pediatric Oncology (SIOP) in patients with BWT.

Results of patients with BWT who progressed or had nonresponsive disease during pre-resection chemotherapy were reported by Shamberger et al (5). Their report described how many of these patients received prolonged courses of escalating chemotherapy and at resection were found to have either anaplastic tumors or lesions with only mature stroma. Based on these findings, the COG is considering a study protocol that will require biopsy or resection of all non-responsive lesions, defined as those with less than 50% reduction in size by CT or MRI following 2 cycles of doxorubicin, dactinomycin, and vincristine. This will allow identification

of patients who have tumors with unfavorable histologic features, i.e. anaplasia or diffuse blastemal histology, that require more intensive chemotherapy. (6,7) [Weirich,Boccon-Gibod] Similarly, some tumors that do not appear to be responding by imaging studies will nonetheless have histologic features that don't portend a poorer prognosis, e.g. mature cells or stromal predominant tumors. These tumors should be removed rather than intensifying or prolonging adjuvant therapy. (8) [Anderson]

The cohort of children with synchronous BWT reported here included 11 children who had complete radiographic response by CT following initial treatment of their Wilms tumors or nephrogenic rests. Size was not predictive of response; in fact, the largest, 7.3 cm lesion, was favorable histology and responded completely to chemotherapy radiographically. The duration of therapy most children received in this cohort was in excess of the standard 18–24 week course of EE-4A or DD4-A recommended for children with unilateral tumors.

Children with synchronous bilateral Wilms tumors or Wilms tumor and contralateral nephrogenic rest that completely responds to initial therapy have a low risk of local relapse. These data support the present recommendation for follow up by serial imaging. Our results, based on a small number of patients are not to be interpreted as supporting continued or prolonged administration of therapy in attempts to achieve a complete response.

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