Original Article

Results of Treatment for Patients With Multicentric or Bilaterally Predisposed Unilateral Wilms Tumor (AREN0534): A Report From the Children's Oncology Group

Peter F. Ehrlich, MD, MSc [1]; Yueh-Yun Chi, PhD[2]; Murali M. Chintagumpala, MD[3]; Fredric A. Hoffer, MD[4]; Elizabeth J. Perlman, MD[5]; John A. Kalapurakal, MD[6]; Brett Tornwall, MA[2]; Anne Warwick, MD [7]; Robert C. Shamberger, MD[8]; Geetika Khanna, MD[9]; Thomas E. Hamilton, MD[8]; Kenneth W. Gow, MD[10]; Arnold C. Paulino, MD [11]; Eric J. Gratias, MD[12]; Elizabeth A. Mullen, MD[8]; James I. Geller, MD [13]; Paul E. Grundy, MD[14]; Conrad V. Fernandez, MD[15,16]; and Jeffrey S. Dome, MD, PhD[17]

BACKGROUND: A primary objective of Children's Oncology Group study AREN0534 (Treatment for Patients With Multicentric or Bilaterally Predisposed, Unilateral Wilms Tumor) was to facilitate partial nephrectomy in 25% of children with bilaterally predisposed unilateral tumors (Wilms tumor/aniridia/genitourinary anomalies/range of developmental delays [WAGR] syndrome; and multifocal and overgrowth syndromes). The purpose of this prospective study was to achieve excellent event-free survival (EFS) and overall survival (OS) while preserving renal tissue through preoperative chemotherapy, completing definitive surgery by 12 weeks from diagnosis, and modifying postoperative chemotherapy based on histologic response. **METHODS:** The treating institution identified whether a predisposition syndrome existed. Patients underwent a central review of imaging studies through the biology and classification study AREN03B2 and then were eligible to enroll on AREN0534. Patients were treated with induction chemotherapy determined by localized or metastatic disease on imaging (and histology if a biopsy had been undertaken). Surgery was based on radiographic response at 6 or 12 weeks. Further chemotherapy was determined by histology. Patients who had stage III or IV disease with favorable histology received radiotherapy as well as those who had stage I through IV anaplasia. **RESULTS:** In total, 34 patients were evaluable, including 13 males and 21 females with a mean age at diagnosis of 2.79 years (range, 0.49-8.78 years). The median follow-up was 4.49 years (range, 1.67-8.01 years). The underlying diagnosis included Beckwith-Wiedemann syndrome in 9 patients, hemihypertrophy in 9 patients, multicentric tumors in 10 patients, WAGR syndrome in 2 patients, a solitary kidney in 2 patients, Denys-Drash syndrome in 1 patient, and Simpson-Golabi-Behmel syndrome in 1 patient. The 4-year EFS and OS rates were 94% (95% CI, 85.2%-100%) and 100%, respectively. Two patients relapsed (1 tumor bed, 1 abdomen), and none had disease progression during induction. According to Response Evaluation Criteria in Solid Tumor 1.1 criteria, radiographic responses included a complete response in 2 patients, a partial response in 21 patients, stable disease in 11 patients, and progressive disease in 0 patients. Posttherapy histologic classification was low-risk in 13 patients (including the 2 complete responders), intermediate-risk in 15 patients, and high-risk in 6 patients (1 focal anaplasia and 5 blastemal subtype). Prenephrectomy chemotherapy facilitated renal preservation in 22 of 34 patients (65%). **CONCLUSIONS:** A standardized approach of preoperative chemotherapy, surgical resection within 12 weeks, and histology-based postoperative chemotherapy results in excellent EFS, OS, and preservation of renal parenchyma. ***Cancer* 2020;126:3516-3525**. © *2020 American Cancer Society*.

KEYWORDS: Beckwith-Wiedemann syndrome (BWS), partial nephrectomy, pediatric, predisposition syndrome, renal tumors, Wilms tumor (WT), Wilms tumor/aniridia/genitourinary anomalies/range of developmental delays (WAGR) syndrome.

INTRODUCTION

The outcome for patients with unilateral, favorable histology (FH) Wilms tumor (WT) is excellent, with 4-year event-free survival (EFS) >85%.[1-4] Most of these children never develop a metachronous tumor, and the overall incidence of renal failure after treatment for most children with unilateral WT is low. However, there is a subpopulation of patients who

Corresponding Author: Peter F. Ehrlich, MD, MSc, Section of Pediatric Surgery, CS Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan 48109 (pehrlich@med.umich.edu).

[1]Section of Pediatric Surgery, CS Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan; [2]Department of Biostatistics, University of Florida, Gainesville, Florida; [3]Department of Pediatrics and Oncology, Texas Children's Hospital Cancer Center at Baylor College of Medicine, Houston, Texas; [4]Department of Radiology, Fred Hutchison Cancer Center, University of Washington, Seattle, Washington; [5]Division of Pediatrics and Oncology, Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois; [6]Department of Radiation Oncology, Northwestern Memorial Hospital, Northwestern University, Chicago, Illinois; [7]Department of Oncology, Walter Reed National Military Medical Center, Washington, District of Columbia; [8]Department of Pediatric Surgery, Boston Children's Hospital and Dana Farber Cancer Center, Boston, Massachusetts; [9]Department of Pediatric Radiology, Washington University of St Louis, St Louis, Missouri; [10]Department of Surgery, University of Washington, Seattle, Washington; [11]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [12]Children's Oncology Group, Philadelphia, Pennsylvania; [13]Division of Hematology/Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [14]Department of Pediatrics, University of Alberta Children's Hospital, Edmonton, Alberta, Canada; [15]Department of Pediatrics, IWK Children's Hospital, Halifax, Nova Scotia, Canada; [16]Department of Bioethics, IWK Children's Hospital, Halifax, Nova Scotia, Canada; [17]Children's National Hospital, George Washington University School of Medicine and Health Sciences, Washington, District of Columbia

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are not only at risk for a unilateral WT but are predisposed to develop metachronous bilateral WT.[5,6] They are also at higher risk of developing renal failure.[7] Examples of patients at risk for a second primary renal tumor include those with *WT1* deletions and mutations, as seen in the WT/aniridia/genitourinary anomalies/range of developmental delays (WAGR), Denys-Drash, and Frasier syndromes; overgrowth syndromes, such as Beckwith-Wiedemann syndrome (BWS); and syndromes associated with other chromosomal anomalies.[8] Many of these children will present with multicentric disease because of an increased incidence of nephrogenic rests compared with patients who have unilateral WT not associated with a genetic predisposition.[9] Porteus et al reviewed the National Wilms Tumor Study Group experience with 53 patients who had BWS; 44 had nephrogenic rests, and 52 of 53 had FH WT. Those who had unilateral disease at presentation reportedly were at a significant risk ($P = .02$) for the development of metachronous contralateral lesions within 4 years (4.5%) compared with a non-BWS control group (0.5%).[10] In their 1993 article, Breslow and colleagues defined the subpopulations at risk for either synchronous or metachronous bilateral tumors, including BWS.[6] A more recent article on BWS refined this risk based on the underlying genetic abnormality.[11]

The incidence of end-stage renal disease (ESRD) is also much higher in these patients. Breslow and colleagues reported a 38% risk of renal failure occurring a median of 20 years after diagnosis of WT in these patients. The highest rate is in those with WT1 deletions. In contrast, the 20-year cumulative incidence of ESRD in the nonsyndromic group for survivors of sporadic unilateral WT was <0.6%. Possible etiologies for ESRD include repeated chemotherapy, surgical therapy and radiotherapy, resulting in the loss of renal units, as well as the known impact of *WT1* mutation on glomerular development and function.

The increased risk of metachronous disease, coupled with the increased risk of ESRD, provided the impetus to maximize sparing of renal units in patients with unilateral WT and an underlying WT predisposition. The Children's Oncology Group (COG) study AREN0534 (Treatment for Patients with Bilateral, Multicentric, or Bilaterally Predisposed Unilateral Wilms Tumor) was the first clinical trial to prospectively enroll and uniformly treat these patients. The objective was to *facilitate partial nephrectomy in lieu of nephrectomy in 25% of children with unilateral tumors and bilateral predisposition syndromes by using prenephrectomy induction chemotherapy*. We report the results of this study.

MATERIALS AND METHODS

Study

The COG study AREN0534 had 3 arms: 1 for the treatment of patients with bilateral WT, 1 for patients with unilateral tumors who were at risk for metachronous disease or multicentric tumors, and 1 for patients with diffuse hyperplastic perilobar nephroblastomatosis.[12] The current report presents the results from children with unilateral tumors who are at risk for metachronous disease (clinical trials.gov identifier, NCT00945009).

Enrollment and Eligibility

The National Cancer Institute Central Institutional Review Board reviewed and approved the study protocol. Where regulatory agreements were in place, the National Cancer Institute Central Institutional Review Board approval was accepted by the local institutional review board. In collaborating sites without such an agreement, the local institutional research ethics board provided approval. All patients or their guardians provided written informed consent before enrollment. Enrollment was required within 14 days of diagnosis or 7 days after starting therapy. To enroll on the unilateral arm of the study of AREN0534, patients were first enrolled on the COG biology and classification study AREN03B2 (Renal Tumors Classification, Biology, and Banking Study; clinicaltrials.gov identifier, NCT00898365), which provided central review of operative notes, diagnostic imaging, and, when available, pathology review.[10-12] Patients had to be aged <30 years at the time of initial diagnosis and must have had 1 of the following conditions: unilateral WT *and* aniridia (WAGR syndrome), BWS, idiopathic hemihypertrophy, Simpson-Golabi-Behmel syndrome, Denys-Drash syndrome (DDS), or other genitourinary anomalies associated with bilateral WT, multicentric WT (at any age), or unilateral WT with contralateral nephrogenic rest(s) (of any size) on imaging in a child aged <1 year.[13] Patients with a solitary kidney could also enroll. Patients could enroll with or without a diagnostic biopsy but were excluded from this arm of the study if they had undergone a nephrectomy at diagnosis. Those who underwent nephrectomy at diagnosis were treated on the standard unilateral protocol. Patients who had a horseshoe kidney or inadequate cardiac or liver function were not eligible.

Staging

Patients received both a local stage designation and an overall disease stage designation. The final local stage was based on the abdominal tumor burden, whereas the disease stage accounted for the presence of distant

TABLE 1. Postchemotherapy Pathology Staging System

Risk	Histology
Low	Completely necrotic Favorable histology
Intermediate	Nephroblastoma, epithelial type Nephroblastoma, stromal type Nephroblastoma, mixed type Nephroblastoma, regressive type Nephroblastoma, focal anaplasia type
High	Nephroblastoma, blastemal type Nephroblastoma, diffuse anaplasia type

TABLE 2. Chemotherapy Regimens for the AREN0534 Study[a]

Regimen	Agents
VAD	Vincristine, dactinomycin, and doxorubicin (maximum 12 wk)
EE-4A	Vincristine and dactinomycin (19 wk)
DD-4A	Vincristine, dactinomycin, and doxorubicin plus radiation therapy (25 wk)
Regimen I	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide plus radiation therapy (28 wk)
UH-1/revised UH-1	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiation (31 wk)

[a]For specific dosing details, please see the Supporting Methods.

metastatic disease. All patients who had an initial biopsy (open, trucut, or fine-needle) were considered to have stage III disease. Open biopsies were strongly encouraged; and, because of the inherent difficulty in diagnosing rests from tumor, fine-needle biopsies were strongly discouraged. The COG and the International Society of Pediatric Oncology (SIOP) staging system have been well described and were used to classify patients who received preoperative chemotherapy (Table 1).[14]

Treatment

The overall strategy of the study was to administer pre-nephrectomy chemotherapy with the aim of shrinking the tumor to allow maximum preservation of the renal parenchyma. Initial induction therapy included vincristine and dactinomycin (regimen EE-4A) if no biopsy was performed and imaging revealed local disease only. Vincristine, dactinomycin, and doxorubicin (regimen VAD) was used if no biopsy was performed and imaging revealed metastatic disease or if the tumor was biopsied and found to have FH WT. If anaplastic histology was identified on biopsy, then regimen UH-1 (vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiation) was mandated by protocol (Table 2). Regimen UH-1 was revised mid-study

TABLE 3. Treatment Regimens at Induction: Unilateral Wilms Tumor With a Predisposition Syndrome to Develop Bilateral Wilms Tumor, Solitary Kidney at Enrollment

Presentation	Initial Imaging	Initial Regimen
Imaging only (no histology)	Localized disease by imaging, no biopsy performed	EE-4A
Imaging only (no histology)	Evidence of distant disease by imaging	VAD
Imaging and biopsy reveal favorable histology	All patients	VAD
Imaging and biopsy reveal unfavorable histology	All patients	UH-1/revised UH-1

Abbreviations: EE-4A, vincristine and dactinomycin (19 weeks); UH-1/revised UH-1, vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiation therapy (31 weeks); VAD, vincristine, dactinomycin, and doxorubicin (maximum, 12 weeks).

because greater than expected toxicities were observed on the companion AREN0321 study for high-risk renal tumors. Initial therapy included two 3-week cycles of chemotherapy (for dosing and regimen, see Supporting Methods). After 2 cycles (approximately 6 weeks), cross-sectional imaging was performed, and a tumor response was assigned by central radiologic review. If partial nephrectomy was deemed feasible by the local institution, surgery was to be undertaken. If the tumors achieved a partial response (PR) but were not amenable to partial nephrectomy, chemotherapy was continued for another 2 cycles. If there was progressive disease (PD) after 2 cycles or, in some tumors, stable disease (SD), a total nephrectomy was performed. If the tumors did not achieve a PR after induction, a total nephrectomy was required by protocol. After 4 cycles of chemotherapy (12 weeks), repeat cross-sectional imaging was performed, and either a partial or total nephrectomy was required. Tables 3-5 list the treatments based on response and histology from enrollment through to definitive surgery. Adverse events were reported using the Common Terminology Criteria for Adverse Events, version 5 (National Cancer Institute).

Radiology Response Criteria

The criteria used to assess tumor response included a reduction in size and the ability to perform a nephron-sparing procedure. Response was based on the Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST).[15] Target lesions were defined as lesions measuring >10 mm within the kidney. If multiple target lesions were present, then the 3 largest lesions were described. Overall response was not modified by extrarenal

TABLE 4. Treatment Regimen For Unilateral Wilms Tumor With a Predisposition Syndrome to Develop Bilateral Wilms Tumor, Solitary Kidney After 2 Cycles (Week-6 Imaging)

Presentation	Initial Imaging	Regimen
CR by imaging	Localized disease by imaging, no biopsy	EE-4A
CR by imaging	Evidence of distant disease by imaging, no biopsy	EE-4A
Initial biopsy revealed FH WT and CR by imaging after 6 wk of chemotherapy		DD-4A
Initial biopsy revealed anaplastic WT and CR by imaging after 6 wk of chemotherapy	Localized abdominal disease by imaging with or without distant metastases	UH-1/revised UH-1
Partial nephrectomy performed at 6 wk; further chemotherapy is based on histology of removed tumor and highest tumor stage		
Histology	**Stage**	**Regimen**
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Regimen I
Blastemal subtype[a]	III-IV	Regimen I + XRT[b]
Diffuse anaplastic WT	I	DD-4A + XRT
Focal anaplastic WT	I-III	DD-4A + XRT
Focal anaplastic WT	IV	UH-1/revisedUH-1 + XRT
Diffuse anaplastic WT	II-IV	UH-1/revised UH-1 + XRT
Completely necrotic tumor	I-II	EE-4A[c]
Intermediate-risk histology	I-II	EE-4A[c]
Completely necrotic tumor[a]	III-IV	DD-4A + XRT
Intermediate-risk histology[a]	III-IV	DD-4A + XRT
Initial treatment was based on imaging alone with less than a partial response; these patients require total nephrectomy		
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Regimen I
Blastemal subtype[a]	III-IV	Regimen I + XRT[b]
Diffuse anaplastic WT	I	DD-4A + XRT
Focal anaplastic WT	I-III	DD-4A + XRT
Focal anaplastic WT	IV	Revised UH-1 + XRT
Diffuse anaplastic WT	II-IV	Revised UH-1 + XRT
Completely necrotic tumor	I-II	EE-4A[c]
Intermediate-risk histology	I-II	EE-4A[c]
Completely necrotic tumor[a]	III-IV	DD-4A + XRT
Intermediate-risk histology[a]	III-IV	DD-4A + XRT
Partial response but partial nephrectomy not feasible; no surgery should be performed		
All	I-IV	Continue with chemotherapy and reevaluate at wk 12

Abbreviations: CR, complete response; DD-4A, vincristine, dactinomycin, and doxorubicin plus radiation therapy (25 weeks); EE-4A, vincristine and dactinomycin (19 weeks); FH, favorable histology; NA, not applicable; UH-1, vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiation therapy (31 weeks); VAD, vincristine, dactinomycin, and doxorubicin (maximum, 12 weeks);WT, Wilms tumor; XRT, radiation therapy.
[a]Biopsy indicates that the patients is stage III for chemotherapy but will *not* require XRT unless they meet other criteria for stage III designation, such as positive lymph nodes. However, patients with anaplastic histology receive XRT.
[b]See Section 4.5 in the Supporting Materials.
[c]See Section 4.2 in the Supporting Materials.

target lesions or nontarget disease. A PR was defined as a decrease ≥30% in the sum of the greatest dimensions of target lesions (which equals a 50% decrease in volume), taking as reference the sum of the baseline dimensions. PD was defined as an increase ≥20% in the sum of the greatest dimensions of target lesions, and SD was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD.

Chemotherapy

Adjuvant therapy was based on a final risk stratification taking into account SIOP tumor stage and histologic response after definitive renal surgery at either 2 or 4 cycles of chemotherapy (Tables 1-5). The details of the chemotherapy regimens have been previously published.[16]

Radiation therapy

Patients with FH tumors who were classified with stage III disease because they underwent biopsy alone did not receive radiation therapy. The other patients with FH tumors who were classified with abdominal stage III, or focal anaplasia stage I through III, or diffuse anaplasia stage I and II disease received flank radiotherapy with 10.8 gray (Gy) (19.8 Gy for those aged ≥16 years).

TABLE 5. Treatment Regimen for Unilateral Wilms Tumor With a Predisposition Syndrome to Develop Bilateral Wilms Tumor, Solitary Kidney After 4 Cycles of Chemotherapy (Week-12 Imaging)

If definitive surgery occurred at end of wk 6 or if there was complete radiologic resolution at end of wk 6		Continue with regimen assigned at end of wk 6
At end of wk 6, therapy was to continue with chemotherapy		
Histology	Stage	Regimen
CR by imaging after 12 wk of chemotherapy	Localized disease by imaging, no biopsy	EE-4A
CR by imaging after 12 wk of chemotherapy	Evidence of distant disease by imaging or even if biopsy performed	EE-4A
Biopsy reveals FH WT and CR by imaging after 12 wk of chemotherapy		DD-4A
Biopsy reveals anaplastic WT and CR by imaging after 12 wk of chemotherapy	Localized disease by imaging	UH-1/revised UH 1
Initial biopsy revealed anaplastic WT and CR by imaging after 12 wk of chemotherapy	Evidence of distant disease by imaging	UH-1/revised UH 1
Nephrogenic rest without WT	NA	EE-4A
At end of wk 6, therapy was to continue with chemotherapy but CR not attained; definitive surgery required either partial nephrectomy if feasible or total nephrectomy if not		
Histology	Stage	Regimen
Blastemal subtype	I	DD-4A
Blastemal subtype	II	Regimen I
Blastemal subtype[a]	III-IV	Regimen I + XRT[b]
Diffuse anaplastic WT	I	DD-4A + XRT
Focal anaplastic WT	I-III	DD-4A + XRT
Focal anaplastic WT	IV	Revised UH-1 + XRT
Diffuse anaplastic WT	II-IV after surgery, no measurable disease	Revised UH-1 + XRT
Nephrogenic rest without WT	NA	EE-4A
Completely necrotic tumor	I-II	EE-4A[c]
Intermediate-risk histology	I-II	EE-4A[c]
Completely necrotic tumor[a]	III-IV	DD-4A + XRT
Intermediate-risk histology[a]	III-IV	DD-4A + XRT

Abbreviations: CR, complete response; DD-4A, vincristine, dactinomycin, and doxorubicin plus radiation therapy (25 weeks); EE-4A, vincristine and dactinomycin (19 weeks); NA, not applicable; UH-1, vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide plus radiation therapy (31 weeks); VAD, vincristine, dactinomycin, and doxorubicin (maximum, 12 weeks);WT, Wilms tumor; XRT, radiation therapy.
[a]Biopsy indicates that the patient us stage III for chemotherapy but will *not* require XRT unless they meet other criteria for stage III designation, such as positive lymph nodes. However, patients with anaplastic histology receive radiation therapy.
[b]See Section 4.5 in the Supporting Materials.
[c]See Section 4.2 in the Supporting Materials.

Patients with stage III diffuse anaplastic histology received 19.8 Gy. Patients required whole-abdomen radiation because of preoperative tumor rupture, peritoneal metastases, or a large intraoperative tumor spill affecting areas outside the tumor bed, as determined by the surgeon. Those with FH received 10.5 Gy, and those with diffuse anaplastic histology received 21 Gy. All patients with stage IV disease who had pulmonary metastasis received whole-lung irradiation to a dose of 12 Gy (10.5 Gy for those aged <12 months), independent of the radiologic response.

Statistical Considerations

The study was opened in July 2009, was monitored by an independent data safety monitoring board, and was closed in June 2015 after reaching the accrual goal. AREN0534 had 3 study arms, and the statistical driver was the bilateral WT arm. A target accrual of 234 patients was required to enroll a minimum of 115 eligible patients with FH, bilateral WT without high-risk (blastemal subtype) features to meet the study's statistical considerations. Interim efficacy monitoring was done at 25%, 50%, and 75% of the expected information using an O'Brien-Fleming boundary (truncated at 3 standard deviations).[17] The unilateral predisposition arm accrued patients as long as the main bilateral WT arm was open. The statistical methods used included Fisher exact tests, Kaplan-Meier estimates, and log-rank tests for the overall survival (OS) and EFS curves. Patient follow-up was current through December 31, 2019.

RESULTS

Patient Characteristics

Thirty-nine patients were enrolled on the unilateral arm. Five patients were excluded for the following reasons: 1 started treatment before signing the consent, 1 did not receive protocol therapy, and 3 had bilateral

renal tumors at diagnosis. Table 6 describes the demographic and clinical characteristics of the 34 remaining patients: 13 were males, 21 were females, and the mean age at diagnosis was 2.79 years (range, 0.49-8.78 years). The median follow-up was 4.49 years (range, 1.67-8.01 years). Underlying diagnoses included 9 patients with BWS, 9 with hemihypertrophy, 10 with multicentric tumors, 2 with WAGR syndrome, 2 with a solitary kidney (1 of these had a previous history of WT without a known predisposition syndrome, and 1 was born with a single kidney also without a predisposition syndrome), 1 with DDS, and 1 with Simpson-Golabi-Behmel syndrome.

TABLE 6. Patient Demographics

Characteristic	Total No. (%)
Sex	
Female	21 (62)
Male	13 (38)
Race	
American Indian or Alaskan	1 (3)
Black or African American	4 (12)
Unknown	3 (9)
White	26 (76)
Ethnicity	
Hispanic or Latino	3 (9)
Not Hispanic or Latino	30 (88)
Unknown	1 (3)
Syndromes	
Beckwith-Wiedemann syndrome	9 (26)
Denys-Drash syndrome	1 (3)
Hemihypertrophy	9 (26)
Simpson-Golabi-Behmel syndrome	1 (3)
Wilms tumor-aniridia syndrome	2 (6)
Miscellaneous	12
Solitary kidney	1 (6)
Age at diagnosis: Median [range], y	2.8 [0.5-8.8]

Tumor Response and Surgical Resection

The tumor response to prenephrectomy chemotherapy among 34 patients who had unilateral, high-risk tumors using the RECIST criteria for the least responsive tumors was CR (n = 2), PR (n = 21), SD (n = 11), and PD (n = 0). Three patients underwent biopsy before starting therapy, and the remaining 31 patients were treated based on clinical and radiographic evidence. Thirty-two patients subsequently underwent surgery; 12 had a complete nephrectomy, and 20 had a partial nephrectomy. There were 11 partial nephrectomies performed after 2 cycles of chemotherapy and 9 after 4 cycles of chemotherapy. Two tumors completely resolved on chemotherapy and required no subsequent surgery. Prenephrectomy chemotherapy facilitated renal preservation in 22 of 34 patients (65%). Table 7 provides the surgical and clinical outcomes based on enrollment eligibility criteria.

Of the 32 patients who underwent surgery, 15 had surgery after 2 cycles (week 6) of chemotherapy and 17 had surgery after 4 cycles (week 12). The 2 patients who had complete resolution of their tumor were considered to have stage I disease and were treated accordingly. Of the 32 patients who underwent a surgical procedure, postsurgical SIOP staging demonstrated that 21 had stage I disease, 4 had stage II disease, 6 had stage III disease (3 because of positive margins), and 1 patient with local stage I was classified with stage IV disease because of pulmonary metastasis. All but the child who was born with a solitary kidney had FH. This child had stage I focal anaplasia. According to SIOP posttherapy histologic classification, there were 13 patients with low-risk histology (including the 2 complete responders), 15 with intermediate-risk histology, and 6 with high-risk histology (1 with focal anaplasia and 5 with blastemal subtype). Of the 10 patients who had multicentric tumors, multiple nodules were examined in 9, and 1 of 9 patients had discordant pathology. In this patient, 1 nodule was low-risk, and the other nodule was intermediate-risk.

There were 22 patients who had a known predisposition syndrome for which routine ultrasound screening would have been expected. Sixteen of these patients had stage I disease, 3 had stage II disease, and 3 had stage III disease. In these patients, based on operative reports, 13 tumors were detected through routine ultrasound. In the other 9 patients, we could not confirm whether routine ultrasound was performed.

Outcomes

The 4-year EFS and OS rates were 94% (95% CI, 85.2%-100%) and 100%, respectively (Fig. 1). There were 2 events, including 1 relapse in a child with BWS. This relapse occurred at 18 months off-therapy and was in the original tumor bed. The initial treatment was with the EE-4A regimen. The relapse histology was FH WT. The second event was a relapse in a child with multicentric disease. This child received prenephrectomy chemotherapy and then underwent partial nephrectomy with a positive margin and postsurgery had high-risk histology. The patient developed a new ipsilateral paraaortic lesion in the original radiation field 6 months after the completion of therapy. There was 1 episode of grade IV toxicity (sinusoidal obstruction syndrome) on regimen DD-4A that was self-limited.

TABLE 7. Surgical and Clinical Outcomes by Enrolment Eligibility on AREN0534

Eligibility	Surgical Procedure	Events
Beckwith-Wiedemann syndrome, N = 9	Partial nephrectomies, n = 8	Relapse/disease progression at 18 mo, n = 1
	Total nephrectomy, n = 1	
Hemihypertrophy, N = 9	Complete resolution, n = 2	None
	Partial nephrectomies, n = 4	
	Total nephrectomies, n = 3	
Multicentric, N = 10	Partial nephrectomies, n = 4	Relapse in para-aortic region with high-risk, positive margin, n = 1
	Total nephrectomies, n = 6	
WAGR, N = 2	Partial nephrectomy, n = 1	None
	Total nephrectomy, n = 1	
Solitary kidney, N = 2	Partial nephrectomies, n = 2	None
Denys-Drash syndrome, N = 1	Total nephrectomy, n = 1	None
Simpson-Golabi-Behmel syndrome, N = 1	Partial nephrectomy, n = 1	None

Abbreviation: WAGR, Wilms tumor/aniridia/genitourinary anomalies/range of developmental delays.

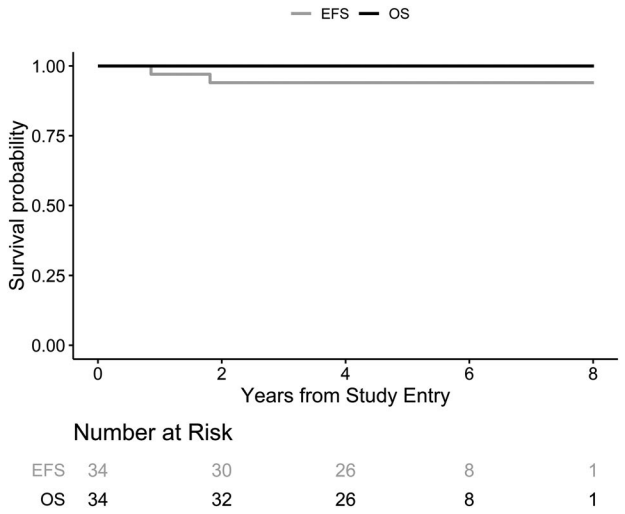

FIGURE 1. Four-year event-free survival (EFS) and overall survival (OS) are illustrated on the unilateral arm of ARENO534. The x-axis represents the years from study, and the y-axis represents survival probability.

DISCUSSION

The study objective for the multicentric or bilaterally predisposed unilateral WT treatment strata was to achieve partial nephrectomy in lieu of nephrectomy in a minimum of 25% of children by using prenephrectomy chemotherapy induction and a prescribed surgical timing approach. We successfully exceeded that aim, with renal preservation occurring in 65% of patients. In addition, we had outstanding outcomes, with 4-year EFS and OS estimates of 94.9% (95% CI, 85.1%-100%) and 100%, respectively.

Several interventions implemented on AREN0534 likely contributed to this improvement in outcome and renal unit preservation. First, chemotherapy was tailored according to postchemotherapy, SIOP-based histologic response. Patients who had diffuse anaplasia and blastemal subtype (high risk) received more intensive chemotherapy compared with patients in previous studies.[18,19] A second intervention implemented on AREN0534 was to mandate definitive surgical resection after 2 or 4 cycles of chemotherapy, which was achieved in all patients. This is in contrast to historical practice, in which definitive surgery was often delayed for months.[20] A third factor that likely contributed to a better outcome is that we targeted a population of infants and children with an elevated risk for developing WT because of their underlying genetic syndrome. Hence many were followed by screening ultrasound, which may have resulted in patients being detected early with low-stage tumors for which both outcomes and the ability to perform renal preservation surgery were predicted to be greater. Sixty-eight percent of patients had stage I disease after induction therapy and surgery (if applicable). This is consistent with previously published SIOP 2001 data, in which 1397 of 2569 patients (55%) were classified with stage I disease after induction chemotherapy.[21]

In this protocol, we used induction prenephrectomy chemotherapy with the goal of nephron-sparing surgery. Our justification was 2-fold. First, these patients have a much higher risk of developing bilateral WT.[6,7,22] Children with these high-risk syndromes also have a higher incidence of nephrogenic rests, which are recognized as precursor lesions to WT.[9,13] Our second justification is that patients who have syndromic WT have a much higher risk of renal failure than those who have nonsyndromic, unilateral WT. Breslow et al reported a renal failure rate from the National Wilms Tumor Study

among patients who had syndromic disease close to 38% at 14 years after diagnosis, and those with the highest risk were patients who had *WT1*-related syndromes.[23-25] In addition, any syndrome associated with metachronous WT carries an increased risk of ESRD because of the need for repeated surgical procedures.

Although it was published after our study closed, the SIOP renal tumor group retrospective study, which was done over 43 years with 34 patients who had BWS and hemihypertrophy, supports our rationale for the study.[26] Nine of those 34 patients underwent renal preservation surgery, and 25 underwent complete nephrectomy. The risk of local relapse was similar in both groups. There were 2 deaths in that study. In a second retrospective, single-center study published in 2012, Romao et al reported on 13 children with predisposition syndromes, including 8 who had syndromes detected by screening and 6 who underwent renal preservation.[27] Those authors also reported excellent outcomes.

A study from the National Wilms Tumor Study Group indicated that WT treatment was as effective in the setting of WAGR syndrome as in the general population of patients with WT.[28] However, long-term survival was decreased in those who had WAGR syndrome because of the high incidence of renal failure. More intensive therapy was recommended. This was concerning because patients with WAGR syndrome have an intrinsic risk of renal failure developing in their teenage years whether or not they develop WT. The results from that study demonstrated excellent disease control without intensifying chemotherapy for the patients with WAGR syndrome.[29] Both in this unilateral cohort and in the bilateral WT cohort reported from AREN0534, patients with WAGR syndrome had outstanding outcomes without intensive therapy.[16] In the current report, our patients with WAGR syndrome received EE-4A, a less toxic regimen, as induction and after surgery. Furthermore, the 5 patients with WAGR on AREN0534 who presented with bilateral WT received the VAD regimen on induction, all were identified as low risk at resection, with stage I or II disease. They subsequently received the EE-4A regimen after resection. All of these children are alive without recurrences or renal dysfunction. This prospective study suggests that patients with WAGR syndrome do not require more intensive therapy. We hope that the renal preservation that the nephron-sparing approach allowed will decrease the long-term risk of ESRD. We plan to perform long-term follow-up in this patient population.

All patients on this study had FH tumors except 1 who was born with a single kidney and no recognized underlying predisposition syndrome. After neoadjuvant treatment, 5 patients with FG WT had the blastemal subtype according to SIOP criteria. Four had stage I disease treated with the DD-4A regimen, and 1 had stage III disease treated with Regimen I (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide plus radiation therapy), and all remain alive. It is possible that, with a larger cohort of cases, anaplasia would have been encountered, but we speculate that a different underlying biology may characterize these subpopulations.

COG renal tumor studies generally require pathology before treatment and study enrollment. The current study was an exception because patients could enroll based on imaging studies alone. The primary reasons to perform a biopsy at initial presentation are to avoid a misdiagnosis of WT, to detect anaplasia, and to identify biomarkers, such as loss of heterozygosity at 1p and 16q or 1q gain. The rate of WT misdiagnosis is low, between 1.6% and 5.5 % for unilateral renal tumors, on SIOP studies.[30] The rate is estimated to be even lower for bilaterally predisposed unilateral tumors; and, in our study, 32 of 34 patients started therapy without a biopsy, and none were misdiagnosed.

The limitations of the study are inherent in its design. Although the EFS and OS reported here are outstanding and are similar to those reported in nonsyndromic unilateral WT, this was not a randomized controlled trial. Second, the study was not designed to determine the effect of this treatment strategy on late effects such as renal failure. Patients will be followed for 10 years to track the rate of renal failure during this extended period. Third, although radiographic criteria were well defined for this study, we cannot be certain that some of the smaller lesions that resolved with neoadjuvant therapy may have been nephrogenic rests. This may be true in the 2 patients in whom the lesions completely resolved. We did not use any of the biomarkers, such as loss of heterozygosity at 1p and 16q or 1q gain, that subsequently have been validated in sporadic unilateral WT to direct therapy. We also note that some patients underwent total nephrectomy at week 6 based on institutional choice rather than continuing with chemotherapy to determine whether a partial nephrectomy could have been performed. Future work will examine the incidence and impact of these biomarkers in the bilateral and unilateral predisposed population. Finally, although we could determine from the operative notes that 13 of 22 patients who had a known predisposition syndrome underwent routine ultrasound screening, in the other 9 patients, it was undocumented, thus

limiting our conclusions regarding whether screening detected early stage tumors.[31,32]

In summary, to our knowledge, this is the largest prospective study of patients with bilaterally predisposed unilateral WT reported to date. This treatment approach, including standardized 2-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis, and histology-based postoperative therapy, showed excellent EFS and OS and preservation of renal parenchyma.

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CONFLICT OF INTEREST DISCLOSURES

Eric J. Gratias is an employee of eviCore Healthcare. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Peter F. Ehrlich: Conceptualization, formal analysis, project administration, methodology, supervision, writing–original, writing–review and editing, data curation, funding acquisition, and investigation. **Yueh-Yun Chi:** Formal analysis and data curation. **Murali M. Chintagumpala:** Conceptualization, formal analysis, methodology, supervision, and writing–review and editing. **Frederic A. Hoffer:** Formal analysis, project administration, methodology, and supervision. **Elizabeth J. Perlman:** Conceptualization, formal analysis, project administration, and data curation. **John A. Kalapurakal:** Conceptualization, formal analysis, project administration, and data curation. **Brett Tornwall:** Formal analysis. **Anne Warwick:** Conceptualization. **Robert C. Shamberger:** Conceptualization, formal analysis, methodology, supervision, and writing–review and editing. **Geetika Khanna:** Formal analysis, project administration, methodology, and supervision. **Thomas E. Hamilton:** Conceptualization; methodology, and supervision. **Ken W. Gow:** Data curation and supervision. **Arnold C. Paulino:** Conceptualization, formal analysis, project administration, and data curation. **Eric J. Gratias:** Conceptualization. **Elizabeth A. Mullen:** Data curation, supervision, validation, and investigation. **James I. Geller:** Data curation, supervision, validation, and investigation. **Paul E. Grundy:** Conceptualization, formal analysis, methodology, and supervision. **Conrad V. Fernandez:** Supervision, funding acquisition, and writing–review and editing. **Jeffrey S. Dome:** Conceptualization, formal analysis, methodology, supervision; funding acquisition, and writing–review and editing.

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