Pediatr Blood Cancer 2013;60:994–1000

REVIEW
Children's Oncology Group's 2013 Blueprint for Research: Renal Tumors

Jeffrey S. Dome, MD, PhD,[1]* Conrad V. Fernandez, MD,[2] Elizabeth A. Mullen, MD,[3] John A. Kalapurakal, MD,[4] James I. Geller, MD,[5] Vicki Huff, PhD,[6] Eric J. Gratias, MD,[7] David B. Dix, MD,[8] Peter F. Ehrlich, MD,[9] Geetika Khanna, MD,[10] Marcio H. Malogolowkin, MD,[11] James R. Anderson, PhD,[12] Arlene Naranjo, PhD,[13] and Elizabeth J. Perlman, MD[14] on behalf of the COG Renal Tumors Committee

Renal malignancies are among the most prevalent pediatric cancers. The most common is favorable histology Wilms tumor (FHWT), which has 5-year overall survival exceeding 90%. Other pediatric renal malignancies, including anaplastic Wilms tumor, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma, have less favorable outcomes. Recent clinical trials have identified gain of chromosome 1q as a prognostic marker for FHWT. Upcoming studies will evaluate therapy adjustments based on this and other novel biomarkers. For high-risk renal tumors, new treatment regimens will incorporate biological therapies. A research blueprint, viewed from the perspective of the Children's Oncology Group, is presented. Pediatr Blood Cancer 2013;60:994–1000.

Key words: clear cell sarcoma; malignant rhabdoid tumor; renal cell carcinoma; Wilms tumor

INTRODUCTION

The overall survival rate for Wilms tumor is 90%. While this figure speaks to the remarkable treatment advances over the past 40 years achieved through successive studies conducted by the National Wilms Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP), it understates the need for further research. Approximately 30% of patients with pediatric renal tumors have survival rates less than 70%, including those with relapsed favorable histology Wilms tumor (FHWT) [1–3], anaplastic Wilms tumor (AHWT) [4], blastemal-type Wilms tumor after pre-operative chemotherapy [5], malignant rhabdoid tumor (MRT) [6,7], and renal cell carcinoma (RCC) [8,9]. Moreover, the high cure rate for Wilms tumor comes at a cost, as 25% of survivors have serious chronic health conditions 25 years from diagnosis [10].

The NWTSG and SIOP studies differ in their approach to the timing of surgical resection. The NWTSG and its successor, the Children's Oncology Group (COG) Renal Tumor Committee, advocate for immediate nephrectomy to ensure accurate histologic diagnosis and staging. The SIOP Renal Tumor Study Group advocates for pre-operative chemotherapy to promote tumor shrinkage and thereby facilitate surgery. Both approaches produce similar overall survival rates. It is important to recognize that because pre-operative chemotherapy alters stage and histology, prognostic factors must be considered in the context of the therapy given. The present article describes the state of the field as seen through the prism of the COG approach and discusses the COG Renal Tumor Committee's blueprint to improve the outcomes of children and adolescents with renal tumors.

STATE OF THE DISEASE - CLINICAL

Overview and Incidence

The kidney is the site of approximately 7% of childhood malignancies, including FHWT, AHWT, clear cell sarcoma of the kidney (CCSK), MRT, RCC, congenital mesoblastic nephroma and other rare tumors. Over 600 subjects per year enroll on the COG AREN03B2 Renal Tumor Classification, Biology, and Banking Study, which captures the majority of pediatric and adolescent renal tumor cases in the United States and Canada. Wilms tumor is the most common pediatric renal tumor, but the incidence of RCC surpasses that of Wilms tumor in adolescents and young adults over age 15 [11].

Staging and Risk Stratification

Several clinical and biological factors contribute to the current COG risk stratification schema. The most important prognostic

[1]Division of Oncology, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, District of Columbia; [2]Division of Pediatric Hematology/Oncology, IWK Health Centre, Halifax, Nova Scotia, Canada; [3]Pediatric Hematology/Oncology, Dana Farber Cancer Institute, Boston, Massachusetts; [4]Department of Radiation Oncology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; [5]Division of Oncology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [6]Department of Genetics, MD Anderson Cancer Center, Houston, Texas; [7]Division of Hematology/Oncology, Children's Hospital at Erlanger, University of Tennessee College of Medicine, Chattanooga, Tennessee; [8]Pediatric Hematology/Oncology, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; [9]Department of Pediatric Surgery, University of Michigan, CS Mott Children's Hospital, Ann Arbor, Michigan; [10]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri; [11]Division of Hematology/Oncology/Bone Marrow Transplant, Children's Hospital of Wisconsin; [12]University of Nebraska Medical Center, Omaha, Nebraska; [13]Department of Biostatistics, Colleges of Medicine and Public Health & Health Professions, University of Florida, Gainesville, Florida; [14]Department of Pathology, Northwestern University's Feinberg School of Medicine and the Robert H. Lurie Cancer Center, Chicago, Illinois

Conflict of interest: Nothing to declare.

*Correspondence to: Dr. Jeffrey S. Dome, MD, PhD, Division of Oncology, Center for Cancer and Blood Disorders, Children's National Medical Center, 111 Michigan Avenue NW, Washington, DC 20010. E-mail: jdome@childrensnational.org

Received 15 October 2012; Accepted 7 November 2012

DOI 10.1002/pbc.24419
Published online 19 December 2012 in Wiley Online Library (wileyonlinelibrary.com).

marker is tumor histology. High-risk histology includes Wilms tumor with anaplasia, CCSK, MRT, and RCC. The second most important determinant is tumor stage. As is the case in most tumors, low stage portends better outcome than high stage. Stage V is a special designation for synchronous bilateral renal tumors, which are associated with outcomes inferior to stage IV tumors (distant metastatic disease). Other factors that contribute to risk stratification for FHWT include patient age, tumor weight, loss of heterozygosity (LOH) at 1p and 16q, and completeness of lung nodule response after 6 weeks of chemotherapy. Based on a compilation of these factors, patients are stratified into five risk categories for enrollment onto present COG treatment studies: very-low risk, low-risk, standard risk, higher-risk favorable histology, and high-risk. These categories are summarized in Table I.

Current Outcome

The outcomes for pediatric renal tumors treated on NWTS-5 are indicated in Table II [4,6,12–14]. An interpretation of overall outcomes for pediatric renal tumors would be incomplete without consideration of late effects of therapy. Although certain subsets of Wilms tumor have outstanding relapse-free (RFS) and overall (OS) survival, 24% of survivors have severe (grade 3–4) chronic health conditions 25 years post-diagnosis [10]. The cumulative incidence of second malignant solid tumors in Wilms tumor survivors at age 40 years is 6.7% [15]. The cumulative incidence of congestive heart failure is 4.4% at 20 years in patients treated with doxorubicin [16]. Female Wilms tumor survivors who received flank radiation are at increased risk for pregnancy-related hypertension, premature labor, fetal malposition and delivery of infants with low birth weights [17]. With reductions of chemotherapy and radiotherapy exposure compared to past treatment protocols, it is expected that the prevalence of late effects will decrease in the future. Nevertheless, even current regimens are predicted to have potential for significant late effects.

STATE OF THE DISEASE—BIOLOGICAL

Molecular Targets

Tremendous strides have been made in our understanding of the molecular genetics of pediatric renal tumors. For Wilms tumor, approximately 15–20% of sporadic tumors have *WT1* mutations or deletions. Because the WT1 transcription factor regulates the expression of multiple genes, there is not a clear, currently drugable molecular target that has emerged for *WT1* mutated tumors. Up to 70% of Wilms tumors have loss of imprinting (LOI) or LOH at 11p15, leading to *IGF2* overexpression [18,19]. Moreover, *IGF2* overexpression appears to be a driver of Wilms tumorigenesis, as evidenced by increased risk of Wilms tumor in individuals with the specific subtype of Beckwith–Wiedemann syndrome associated with *IGF2* LOI and the development of Wilms tumors in transgenic mice overexpressing *Igf2* in the setting of *Wt1* ablation [20,21]. Agents targeting the IGF1R pathway are therefore attractive therapeutic targets for Wilms tumor. Approximately 35% of Wilms tumors have mutations in *CTNNB1* (β-catenin) or *WTX*, which are components of the WNT signaling pathway [22]. Additional targets of interest, based on tumor tissue protein expression, specific molecular interrogation, RNA expression profiling, pre-clinical activity in xenograft models, and clinical responses in phase I and II studies, include antiangiogenic compounds, aurora-A-kinase, mTOR, c-Met, JAK2, and telomerase inhibitors, as well as agents functioning independent of p53 (75% of anaplastic Wilms tumors have p53 mutations). Of note, the general category of anti-mitotic drugs demonstrates anti-Wilms efficacy in xenograft models [23–25].

Malignant rhabdoid tumor is caused by deletions and mutations of the *SMARCB1* gene on chromosome 22q (also referred to as *INI1*, *BAF47*, and *SNF5*) [26–28]. *SMARCB1* encodes a member of the SWI/SNF chromatin remodeling complex, which regulates transcription by controlling access of transcription machinery to gene promoters [29]. The genes involved in the development of rhabdoid tumor remain to be elucidated, but several

TABLE I. Current COG Risk Stratification for Pediatric Renal Tumors

Patient age	Tumor weight	Stage, histology	LOH at both 1p and 16q	Rapid lung nodule response	Risk group	Treatment study
<2 years	<550 g	I, FH	Any	N/A	Very low	AREN0532
<2 years	≥550 g	I, FH	None	N/A	Low	None
≥2 years	Any	I, FH	None	N/A	Low	None
Any	Any	II, FH	None	N/A	Low	None
≥2 years	Any	I, FH	LOH	N/A	Standard	AREN0532
Any	≥550 g	I, FH	LOH	N/A	Standard	AREN0532
Any	Any	II, FH	LOH	N/A	Standard	AREN0532
Any	Any	III, FH	None	Any	Standard	AREN0532
Any	Any	III, FH	LOH	Any	Higher-FH	AREN0533
Any	Any	IV, FH	LOH	Any	Higher-FH	AREN0533
Any	Any	IV, FH	None	Yes	Standard	AREN0533
Any	Any	IV, FH	None	No	Higher-FH	AREN0533
Any	Any	V, FH, AH	Any	Any	Bilateral	AREN0534
Any	Any	I-IV, AH, CCSK, RCC, MRT	Any	Any	High	AREN0321

FH, favorable histology Wilms tumor; AH, anaplastic histology Wilms tumor; CCSK, clear cell sarcoma of the kidney; RCC, renal cell carcinoma; MRT, malignant rhabdoid tumor.

TABLE II. Outcomes for Pediatric Renal Tumors on NWTS-5

Histology and stage	4-year relapse-free survival rate (%)	4-year overall survival rate (%)
Favorable histology		
I (<24 months/tumor weight <550g , nephrectomy only)[a]	84	98
I/II, no LOH	91	98
I/II, LOH 1p and 16q	75	91
III/IV, no LOH	83	92
III/IV, LOH 1p and 16q	66	78
V, any LOH	61	81
Diffuse anaplastic histology		
I	68	79
II	83	82
III	65	67
IV	33	33
V	25	42
Clear cell sarcoma[a]		
I	100	100
II	87	97
III	73	89
IV	40	45
Malignant rhabdoid tumor		
I	50	50
II	33	33
III	33	33
IV	21	21
Renal cell carcinoma[b]		
I	—	92
II	—	85
III	—	73
IV	—	14

[a]Outcomes are expressed as 5-year EFS and OS. [b]For renal cell carcinoma, outcomes are expressed in terms of overall survival [8].

lines of evidence indicate that these tumors have altered expression of members of the $p16^{INK4A}$/CyclinD1/E2F pathway, which regulates the cell cycle. Agents targeting the cyclin D1 pathway, as well as epigenetic modifiers that affect chromatin remodeling are of interest for rhabdoid tumor. Additional targets of interest, based on pre-clinical activity in xenograft models and clinical responses in phase I/II studies, include angiogenesis inhibitors and aurora-A-kinase inhibitors.

The biology of pediatric RCC is distinct from its adult counterpart. Whereas the vast majority of adult RCC have clear cell histology associated with *VHL* mutations, this type of RCC is very rare in children and adolescents. Only 1 of 120 children with RCC enrolled on the COG AREN03B2 Renal Tumor Biology, Classification, and Banking Study have clear cell RCC. The most common type of pediatric RCC is the translocation subtype, which harbors translocations involving genes that encode members of the microophthalmia (MiTF) family of transcription factors. The most commonly involved gene is *TFE3* on chromosome Xp11, which can fuse to several partners including *ASPL* (17q25), *PRCC* (1q21), *PSF* (1p34), *NonO* (Xq12), and *CLTC* (17q23) [30]. Translocation RCC continues to present through adulthood, with recent estimates suggesting that translocation RCC accounts for approximately 1–5% of adult renal cell carcinoma. Biological targets of interest have now been identified and include c-Met [31], mTOR, and VEGFR. A phase II study of the c-MET inhibitor ARQ197 (tivantinib) in this group of cancers did not produce objective responses in the few patients treated [32]. Reports of disease stabilization with mTOR inhibitors are available [33,34]. Anecdotal evidence of response of translocation RCC to VEGF receptor tyrosine kinase inhibitors is growing, with frequent objective responses and rare durable complete remissions, predominantly with sunitinib therapy, in both pediatric and adult patients [33,35–37].

Molecular Prognostic factors

Molecular markers that have been described with prognostic implications include loss of heterozygosity (LOH) 1p and 16q, gain at 1q, telomerase expression, and certain gene expression profiles [12,38,39]. LOH at chromosomes 1p and 16q were prospectively analyzed as part of the NWTS-5 trial. LOH at both 1p and 16q was associated with decreased event-free and overall survival for FHWT [12]. Based on this observation, current COG studies are assessing whether augmenting therapy for patients with stage I–IV FHWT and LOH will improve outcomes.

MAJOR RECENT FINDINGS

Renal Tumor Biology, Classification, and Banking Study (AREN03B2)

Enrollment on this study has averaged more than 600 patients per year; nearly all cases have had central pathology, surgery, and radiology reviews of CT scans in real time, with a turnaround time <7 days. It is also feasible to conduct molecular LOH analysis with a 2-week turnaround time. The central pathology reviews continue to detect cases of high-risk renal tumors (most notably anaplastic histology) that are not detected by institutional pathologists and incorrectly staged tumors, highlighting the benefit of central review. A review of the first 3,000 patients enrolled on AREN03B2 revealed that 35% of cases of diffuse anaplastic Wilms tumor were not identified by the local pathologist. A manuscript on the value of CT scan for detecting tumor thrombus was published [40] and another on the predictive value of CT scan for detecting tumor rupture is in press. Abstracts on the epidemiology of pediatric RCC and surgical approach were recently presented at national meetings and will be submitted for publication shortly.

Clinically Significant Subsets of Favorable Histology Wilms Tumor Have Been Identified Based on Gene Expression Patterns (AREN03B1)

Two hundred twenty-four FHWT from patients enrolled onto NWTS-5 were evaluated for (i) global gene expression patterns, (ii) *WT1*, *CTNNB1*, *WTX* mutation status, and (iii) 11p15 copy number and methylation pattern. Five subsets were identified showing distinct differences in pathologic and clinical features; these findings were validated in 100 additional FHWT. The gene expression pattern of each subset was then compared with published gene expression profiles during normal renal development. A novel subset (Subset 1) consists of epithelial FHWT in infants. These lack *WT1*, *CTNNB1*, and *WTX* mutations and nephrogenic rests and none recurred. They display a gene expression pattern of the post-induction nephron. Three subsets (Subsets 2–4) are characterized by low *WT1* expression and intralobar nephrogenic rests.

These differ from one another in their frequency of *WT1* and *CTNNB1* mutations, age at presentation, relapse rate, and in the developmental timing of their development. The largest subset (Subset 5) is characterized by biallelic methylation of the imprint control region 1 of 11p15, and both intralobar and perilobar nephrogenic rests. These data provide a biologic explanation for the clinical and pathologic heterogeneity seen within WT, and enable the future development of subset-specific therapeutic strategies [41].

Genetic and Epigenetic Features May Be Used to Better Stratify Patients Eligible for Treatment Without Adjuvant Chemotherapy (AREN10B1)

Patients <24 months of age with Stage I FHWT weighing <550 g are defined as having very low risk WT (VLRWT) and were treated with surgery alone on NWTS-5. The study closed early due to a relapse rate that exceeded the pre-defined stopping rules. The overall survival rate was outstanding, but patients with relapse were exposed to doxorubicin and radiation therapy that they otherwise would not have received [42,43]. It would be advantageous to identify biological prognostic factors to select patients who do not require adjuvant therapy. Gene expression analyses have identified subgroups of VLRWT patients with distinct prognosis. Subsets 1 and 2 (described above) each account for 30% of VLRWT. None of the patients with Subset 1 VLRWT treated on NWTS-5 relapsed, even when they did not receive adjuvant chemotherapy [44]. By contrast, patients with Subset 2 VLRWT had increased risk of relapse when they were not treated with chemotherapy, though patients with Subset 2 tumors had an excellent outcome when they received adjuvant chemotherapy [44].

Expanding on the above analysis, all VLRWT registered on NWTS-5 who did not receive adjuvant chemotherapy were analyzed for LOH at 11p15 and for WT1 mutation (both of which were features of Subset 2 tumors) and retention of imprinting (ROI) at 11p15 (which characterizes Subset 1 tumors). In this study, LOH, as determined by 11p15 methylation analysis, was significantly associated with relapse in VLRWT ($P < 0.0001$) as were *WT1* abnormalities ($P = 0.004$) [45]. If these results are validated in an independent cohort of patients, it would be worthwhile to conduct a clinical trial that uses molecular genetic factors rather than the arbitrarily defined clinical factors of patient age and tumor weight to identify patients with stage I FHWT who do not require adjuvant therapy. It is anticipated that such a trial would expand the number of patients who would be candidates to be treated with surgery only.

Chromosome 1q Gain May Serve as a New Prognostic Marker for FHWT (AREN11B3)

A number of large studies using convenience samples consistently showed a frequency of 1q gain in FHWT of 25% and a strong association between 1q gain and relapse, with relative risks of 2.5, 2.75, and 3.14 [46–49]. These studies were based on cytogenetic, classic CGH, array-CGH, and gene expression analyses. The combination of high prevalence and high relative risk indicates a potentially strong biomarker for relapse. The immediate clinical impact of analysis of 1q gain (assuming a conservative projected relative risk of at least 2.0 and a prevalence of 25%) is the accurate prediction of at least 40% of relapses, compared with the current ability to detect 9% of relapses using LOH at chromosome 1p and 16q. To assess the prognostic significance of 1q gain in a uniformly treated group of patients, 226 evaluable samples from NWTS-4 were assessed for 1q gain using multiplex ligation-dependent probe amplification (MLPA). Consistent with previous studies, 25% of samples demonstrated 1q gain. The 8-year RFS was 76% (95% CI 63%, 85%) for those with 1q gain and 93% (95% CI 87%, 96%) for those who lacked 1q gain ($P = 0.0024$). The 8-year OS was 89% (95% CI 78%, 95%) for those with 1q gain, and 98% (95% CI 94%, 99%) for those who lacked 1q gain ($P = 0.0075$). There were too few events to analyze the effect of 1q gain within stage subsets. However, there was no indication that 1q gain correlated with disease stage (Gratias, manuscript in preparation). Confirmatory analysis of 1,700 NWTS-5 samples is in progress and will enable multi-variate analysis that takes into account other clinical and biological risk factors. If the prognostic significance of 1q gain is confirmed, future clinical trials could incorporate 1q gain into a new risk stratification schema for FHWT.

STRATEGIC APPROACH

Newly Diagnosed Population

To prioritize research initiatives, renal tumors may be classified by RFS and the potential for acute and long-term treatment-related adverse effects (Table III). Four main categories of patients are defined:

Excellent RFS and low potential for late effects: Given the number of patients available for study, it is unlikely that outcomes can be measurably improved using classic clinical trial designs. Most patients in this category are enrolled on the biology and classification study (AREN03B2), but are not treated on a therapeutic study. Subsets of patients will have compelling biomarkers that suggest that a change in therapy may be justified. For example, ROI at chromosome 11p15 may identify patients who do not require adjuvant therapy at all, as described in the Major Recent Findings Section. In addition, application of 1q gain findings may identify apparently low risk patients that should be considered for augmented therapy.

Excellent RFS and moderate-high potential for late effects: For these patients, there is opportunity to pursue a reduction in therapy. If 1q gain is validated as a prognostic factor, a new primary aim may be to eliminate doxorubicin from patients with stage III FHWT without 1q gain.

Good RFS and moderate to high potential for late effects: Here, there is opportunity to improve tumor control and decrease therapy-related toxicity. The plan for this category of patients involves therapeutic studies that either augment or reduce therapy, depending on the strength of the scientific rationale for a change in treatment.

Unsatisfactory RFS: With RFS <75%, the priority is to develop novel treatment regimens and targeted therapy based on biological studies and pre-clinical testing.

Relapsed Wilms Tumor

Patients with relapsed Wilms tumor may be divided into three risk groups (standard, high, and very high) according to overall survival rates after salvage therapy [50]. The standard risk group

TABLE III. Pediatric Renal Tumors by RFS and Potential for Late Effects

	Potential for late effects	
Relapse-free survival (NWTS-5)	Low	Moderate to high
Excellent (≥85%)	Stage I/II FHWT, LOH− (210 patients per year)	Stage I/II CCSK Stage III FHWT, LOH− (125 patients per year)
Good (75–84%)		Stage IV FHWT, LOH− Stage II AHWT Stage III CCSK (70 patients per year)
Unsatisfactory (<75%)	Stage I/II FHWT, LOH+ Stage I AHWT Stage III/IV RCC (35 patients per year)	Stage III/IV FHWT, LOH+ Stage III/IV AHWT Stage V WT Stage IV CCSK Stage I–IV MRT Relapsed FHWT (125 patients per year)

includes patients with non-anaplastic Wilms tumor with relapse after therapy with only vincristine and/or dactinomycin. These patients are expected to have survival rates in the 70–80% range [51]. The high-risk group includes patients with non-anaplastic Wilms tumor with relapse after therapy with three or more agents, typically vincristine, dactinomycin, doxorubicin, and cyclophosphamide. These patients are expected to have survival rates in the 40–50% range [2]. The very high-risk group includes patients with recurrent anaplastic or blastemal-type WT. These patients are expected to have survival rates in the 10% range [4,52]. Improved outcomes for the high-risk and very-high risk groups will likely require novel treatment regimens that combine standard chemotherapy with molecularly targeted agents.

KEY TRIALS TO BE PURSUED BY COG

Front-Line Study for Favorable Histology Wilms Tumor

A single, multi-strata clinical trial is planned for patients with FHWT. The centerpiece of the trial is a new risk stratification system that uses ROI at 11p15 and gain of chromosome 1q as biomarkers. The plans outlined below are contingent upon successful validation of these prognostic markers using independent patient cohorts.

The first stratum will include patients with stage I FHWT. The aim will be to determine whether patients whose tumors have ROI at 11p15 will have outstanding overall survival without adjuvant chemotherapy. The rationale for this study is based on the results outlined above for the AREN10B1 study. Among NWTS-5 patients treated with nephrectomy only, there were no relapses in patients with retention of heterozygosity at 11p15 and without WT1 mutation. Conversely, loss of imprinting at 11p15 was associated with relapse.

The second stratum will include patients with stage III FHWT without gain of chromosome 1q and without LOH at 1p and 16q. The objective will be to determine whether doxorubicin can be eliminated from front-line therapy for such patients. Long-term follow-up data on NWTS-3 and -4 indicate that doxorubicin contributes to relapse-free survival, but not overall survival [53,54]. Moreover, the SIOP-2001 randomized patients with stage II and III disease with intermediate-risk histology to receive or not receive doxorubicin. The results showed no difference in overall survival with or without doxorubicin [55]. Based on these findings, we propose to evaluate whether excellent RFS and OS can be preserved when doxorubicin is omitted from the treatment of patients without 1q gain, estimated to be 75% of the stage III population.

The third stratum will include patients with FHWT and gain of chromosome 1q, with the objective of assessing whether augmentation of therapy improves RFS. For patients with stage I/II FHWT, doxorubicin will be added to vincristine and dactinomycin therapy. For patients with stage III/IV FHWT, cyclophosphamide and etoposide will be added to vincristine, dactinomycin, and doxorubicin. As outlined in the Recent Findings Section above, the rationale for augmenting therapy is that previous studies have found that 1q gain is observed in 25% of Wilms tumor samples and is associated with a RR of recurrence of approximately 2.5–3.

An additional objective for patients with stage IV disease will be to determine the feasibility of intensity modulated radiation therapy (IMRT) in children receiving whole lung and liver irradiation. The goal would be to reduce the amount of radiation delivered to the heart, liver, and possibly the thyroid gland. To limit XRT exposure, the AREN0533 study is withholding lung XRT for patients with stage IV FHWT whose lung nodules resolve by week 6 of treatment. So far on AREN0533, approximately 40% of patients are not receiving XRT. To reduce XRT exposure in the patients who do not have a rapid response, COG plans to study the feasibility of IMRT. The use of IMRT in conjunction with respiratory gating techniques has enabled the safer delivery of higher doses of RT to the thoracic structures such as lung and pleura in adult patients with lung cancer and mesothelioma, respectively [56,57]. The implementation, compliance, and efficacy of whole lung IMRT will have to be evaluated carefully before it can be considered as a standard alternative to conventional whole lung irradiation in children with Wilms tumor.

Therapy for Bilateral Wilms Tumor (BWT)

BWT presents the dual challenge of maintaining tumor control and preserving nephrons. The 8-year EFS for BWT was only 74% among patients enrolled on NWTS-4 [13]. Moreover, the cumulative rate of end-stage renal disease in long-term survivors of BWT without syndromic features was 12% [58]. The COG AREN0534 study is attempting to decrease the rate of recurrence

and enhance nephron sparing surgery by treating all patients with doxorubicin in addition to vincristine and dactinomycin for the first 6–12 weeks of therapy. Nephron-sparing surgery is mandated by week 12 and post-surgical therapy is tailored according to histology using the SIOP post-chemotherapy histologic risk classification schema. This study is expected to continue until 2015.

Therapy for Relapsed FHWT and Other High-Risk Renal Tumors

The NWTS-5 protocol for high-risk recurrent FHWT used cyclophosphamide/etoposide alternating with carboplatin/etoposide. The 4-year RFS and OS were only 42% and 48%, respectively [2]. A novel randomized phase 2 study design using a decision analysis approach [59–61] will be conducted to evaluate the contribution of a biological agent to a chemotherapy backbone that incorporates topotecan, recently shown to be active in recurrent Wilms tumor [62], in addition to other active agents (ifosfamide, carboplatin, etoposide, and cyclophosphamide) The selection of the biological agent will depend on results of ongoing COG phase 1 and 2 studies of agents targeting IGF1R, aurora A kinase, c-MET, JAK2, and the multi-targeted/VEGF receptor kinase inhibitors. A similar approach to incorporate molecularly targeted therapy is envisioned for frontline therapeutic trials for diffuse anaplastic Wilms tumor and malignant rhabdoid tumor.

Therapy for Translocation RCC

COG is planning a prospective therapeutic study of translocation RCC, a renal tumor that affects primarily adolescents and young adults. The study would be conducted in collaboration with the Eastern Cooperative Oncology Group (ECOG) and other adult cooperative groups. Based on preliminary data from retrospective studies that sunitinib has activity against translocation RCC [33,35–37], the efficacy of sunitinib or newer generation multi-tyrosine kinase inhibitors will be studied prospectively. The feasibility of conducting a Phase 2 study in this rare disease through inter-group cooperation will be determined, the clinical description of translocation RCC will be refined, and the surgical and radiological guidelines and practices will be characterized.

ACKNOWLEDGMENT

The research was supported by grants from the National Institutes of Health to the National Wilms Tumor Study Group (CA54498 and CA42326) and the Children's Oncology Group (CA98543, CA98413, and CA114766).

REFERENCES

1. Dome JS, Liu T, Krasin M, et al. Improved survival for patients with recurrent Wilms tumor: The experience at St. Jude Children's Research Hospital. J Pediatr Hematol Oncol 2002;24:192–198.
2. Malogolowkin M, Cotton CA, Green DM, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 2008;50:236–241.
3. Ha TC, Spreafico F, Graf N, et al. An international strategy to determine the role of high dose therapy in recurrent Wilms' tumour. Eur J Cancer 4: 2012.
4. Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms' tumor: Results from the fifth National Wilms' Tumor Study. J Clin Oncol 2006;24:2352–2358.
5. Graf N, van Tinteren H, Bergeron C, et al. Characteristics and outcome of stage II and III non-anaplastic Wilms' tumour treated according to the SIOP trial and study 93-01. Eur J Cancer 2012;48:3240–3248.
6. Tomlinson GE, Breslow NE, Dome J, et al. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: Age at diagnosis as a prognostic factor. J Clin Oncol 2005;23:7641–7645.
7. van den Heuvel-Eibrink MM, van Tinteren H, Rehorst H, et al. Malignant rhabdoid tumours of the kidney (MRTKs), registered on recent SIOP protocols from 1993 to 2005: A report of the SIOP renal tumour study group. Pediatr Blood Cancer 2011;56:733–737.
8. Geller JI, Dome JS. Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer 2004;101:1575–1583.
9. Indolfi P, Terenziani M, Casale F, et al. Renal cell carcinoma in children: A clinicopathologic study. J Clin Oncol 2003;21:530–535.
10. Termuhlen AM, Tersak JM, Liu Q, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 2011;57:1210–1216.
11. Howlader NNA, Krapcho M, Neyman N, et al., SEER Cancer Statistics Review, 1975–2008, 2011; http://seer.cancer.gov/csr/1975_2008/csr/1975_2008/
12. Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: A report from the National Wilms Tumor Study Group. J Clin Oncol 2005;23:7312–7321.
13. Hamilton TE, Ritchey ML, Haase GM, et al. The management of synchronous bilateral Wilms tumor: A report from the National Wilms Tumor Study Group. Ann Surg 2011;253:1004–1010.
14. Seibel NL, Sun J, Anderson JR, et al. Outcome of clear cell sarcoma of the kidney (CCSK) treated on the National Wilms Tumor Study-5 (NWTS). J Clin Oncol 2006;24:502S.
15. Breslow NE, Lange JM, Friedman DL, et al. Secondary malignant neoplasms after Wilms tumor: An international collaborative study. Int J Cancer 2009;127:657–666.
16. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: A report from the National Wilms' Tumor Study group. J Clin Oncol 2001;19:1926–1934.
17. Green DM, Lange JM, Peabody EM, et al. Pregnancy outcome after treatment for Wilms tumor: A report from the national Wilms tumor long-term follow-up study. J Clin Oncol 2010;28:2824–2830.
18. Steenman MJC, Rainier S, Dobry CJ, et al. Loss of imprinting of IGF2 is linked to reduced expression and abnormal methylation of H19 in Wilms' tumour. Nat Genetics 1994;7:433–439.
19. Fukuzawa R, Breslow NE, Morison IM, et al. Epigenetic differences between Wilms' tumours in white and east-Asian children. Lancet 2004;363:446–451.
20. Hu Q, Gao F, Tian W, et al. Wt1 ablation and Igf2 upregulation in mice result in Wilms tumors with elevated ERK1/2 phosphorylation. J Clin Invest 2010;121:174–183.
21. Shuman CBJ, Smith AC, Weksberg R. Beckwith–Wiedemann syndrome. In: RABT Pagon, CR Dolan, editors. GeneReviews (Internet). Seattle: University of Washington; 2010.
22. Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: Mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. Genes Chromosomes Cancer 2008;47:461–470.
23. Maris JM, Morton CL, Gorlick R, et al. Initial testing of the aurora kinase A inhibitor MLN8237 by the pediatric preclinical testing program (PPTP). Pediatr Blood Cancer 2010;55:26–34.
24. Peterson JK, Tucker C, Favours E, et al. In vivo evaluation of ixabepilone (BMS247550), a novel epothilone B derivative, against pediatric cancer models. Clin Cancer Res 2005;11:6950–6958.
25. Carol H, Lock R, Houghton PJ, et al. Initial testing (stage 1) of the kinesin spindle protein inhibitor ispinesib by the pediatric preclinical testing program. Pediatr Blood Cancer 2009;53:1255–1263.
26. Versteege I, Sevenet N, Lange J, et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 1998;394:203–206.
27. Biegel JA, Zhou JY, Rorke LB, et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res 1999;59:74–79.
28. Eaton KW, Tooke LS, Wainwright LM, et al. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer 2010;56:7–15.
29. Roberts CW, Biegel JA. The role of SMARCB1/INI1 in development of rhabdoid tumor. Cancer Biol Ther 2009;8:412–416.
30. Argani P, Ladanyi M. Translocation carcinomas of the kidney. Clin.Lab Med 2005;25:363–378.
31. Tsuda M, Davis IJ, Argani P, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 2007;67:919–929.
32. Wagner AJ, Goldberg JM, Dubois SG, et al. Tivantinib (ARQ 197), a selective inhibitor of mesenchymal-epithelial transition factor, in patients with microphthalmia transcription factor-associated tumors: Results of a multicenter phase 2 trial. Cancer 2012;118:5894–5902.
33. Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): A report from the Juvenile RCC Network. Ann Oncol 2010; 21:1834–1838.
34. Parikh J, Coleman T, Messias N, et al. Temsirolimus in the treatment of renal cell carcinoma associated with Xp11.2 translocation/TFE gene fusion proteins: A case report and review of literature. Rare Tumors 2009;1:e53.
35. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. Cancer 2010;116:5219–5225.
36. Malouf GG, Camparo P, Molinie V, et al. Transcription factor E3 and transcription factor EB renal cell carcinomas: Clinical features, biological behavior and prognostic factors. J Urol 2011;185:24–29.
37. Liu YC, Chang PM, Liu CY, et al. Sunitinib-induced nephrotic syndrome in association with drug response in a patient with Xp11.2 translocation renal cell carcinoma. Jpn J Clin Oncol 2011;41:1277–1281.
38. Dome JS, Bockhold CA, Li SM, et al. High telomerase RNA expression level is an adverse prognostic factor for favorable-histology Wilms' tumor. J Clin Oncol 2005;23:9138–9145.
39. Huang CC, Gadd S, Breslow N, et al. Predicting relapse in favorable histology Wilms tumor using gene expression analysis: A report from the Renal Tumor Committee of the Children's Oncology Group. Clin Cancer Res 2009;15:1770–1778.
40. Khanna G, Rosen N, Anderson JR, et al. Evaluation of diagnostic performance of CT for detection of tumor thrombus in children with Wilms tumor: A report from the Children's Oncology Group. Pediatr Blood Cancer 2011;58:551–555.
41. Gadd S, Huff V, Huang CC, et al. Clinically relevant subsets identified by gene expression patterns support a revised ontogenic model of Wilms tumor: A Children's Oncology Group Study. Neoplasia 2012;14:742–756.
42. Green DM, Breslow NE, Beckwith JB, et al. Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: A report from the National Wilms' Tumor Study Group. J Clin Oncol 2001;19:3719–3724.
43. Shamberger RC, Anderson JR, Breslow NE, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. Ann Surg 2010;251:555–558.
44. Sredni ST, Gadd S, Huang CC, et al. Subsets of very low risk Wilms tumor show distinctive gene expression, histologic, and clinical features. Clin Cancer Res 2009;15:6800–6809.
45. Perlman EJ, Grundy PE, Anderson JR, et al. WT1 mutation and 11P15 loss of heterozygosity predict relapse in very low-risk wilms tumors treated with surgery alone: A children's oncology group study. J Clin Oncol 2011;29:698–703.
46. Natrajan R, Williams RD, Hing SN, et al. Array CGH profiling of favourable histology Wilms tumours reveals novel gains and losses associated with relapse. J Pathol 2006;210:49–58.
47. Natrajan R, Little SE, Sodha N, et al. Analysis by array CGH of genomic changes associated with the progression or relapse of Wilms' tumour. J Pathol 2007;211:52–59.
48. Hing S, Lu YJ, Summersgill B, et al. Gain of 1q is associated with adverse outcome in favorable histology Wilms' tumors. Am J Pathol 2001;158:393–398.

49. Lu YJ, Hing S, Williams R, et al. Chromosome 1q expression profiling and relapse in Wilms' tumour. Lancet 2002;360:385–386.
50. Spreafico F, Pritchard Jones K, Malogolowkin MH, et al. Treatment of relapsed Wilms tumors: lessons learned. Expert Rev Anticancer Ther 2009;9:1807–1815.
51. Green DM, Cotton CA, Malogolowkin M, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine and actinomycin D: A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 2007;48:493–499.
52. Reinhard H, Schmidt A, Furtwangler R, et al. Outcome of relapses of nephroblastoma in patients registered in the SIOP/GPOH trials and studies. Oncol Rep 2008;20:463–467.
53. Breslow NE, Ou SS, Beckwith JB, et al. Doxorubicin for favorable histology, Stage II–III Wilms tumor: Results from the National Wilms Tumor Studies. Cancer 2004;101:1072–1080.
54. Green DM. The treatment of stages I–IV favorable histology Wilms' tumor. J Clin Oncol 2004; 22:1366–1372.
55. Pritchard Jones K, Graf N, Bergeron C, et al. Doxorubicin can be safely omitted from the treatment of Stage II/III intermediate risk histology Wilms tumour: Results of the SIOP 2001 randomized trial. Pediatr Blood Cancer 2011;57:741.
56. Grills IS, Yan D, Martinez AA, et al. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: A comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. Int J Radiat Oncol Biol Phys 2003;57:875–890.
57. Schwarz M, Alber M, Lebesque JV, et al. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int.J Radiat Oncol Biol Phys 2005;62:561–570.
58. Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: Results from the National Wilms tumor study group and the United States Renal Data System. J Urol 2005;174:1972–1975.
59. Berry DA, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: A decision analysis. Stat Med 1995;14:231–246.
60. Berry DA. Bayesian clinical trials. Nat Rev Drug Discov 2006;5:27–36.
61. Berry DA. Adaptive clinical trials in oncology. Nat Rev Clin Oncol 2011;9:199–207.
62. Metzger ML, Stewart CF, Freeman BB III, et al. Topotecan is active against Wilms' tumor: Results of a multi-institutional phase II study. J Clin Oncol 2007;25:3130–3136.