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REVIEW ARTICLE

Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration

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ABSTRACT

Clinical trials in Wilms tumor (WT) have resulted in overall survival rates of greater than 90%. This achievement is especially remarkable because improvements in disease-specific survival have occurred concurrently with a reduction of therapy for large patient subgroups. However, the outcomes for certain patient subgroups, including those with unfavorable histologic and molecular features, bilateral disease, and recurrent disease, remain well below the benchmark survival rate of 90%. Therapy for WT has been advanced in part by an increasingly complex risk-stratification system based on patient age; tumor stage, histology, and volume; response to chemotherapy; and loss of heterozygosity at chromosomes 1p and 16q. A consequence of this system has been the apportionment of patients into such small subgroups that only collaboration between large international WT study groups will support clinical trials that are sufficiently powered to answer challenging questions that move the field forward. This article gives an overview of the Children's Oncology Group and International Society of Pediatric Oncology approaches to WT and focuses on four subgroups (stage IV, initially inoperable, bilateral, and relapsed WT) for which international collaboration is pressing. In addition, biologic insights resulting from collaborative laboratory research are discussed. A coordinated expansion of international collaboration in both clinical trials and laboratory science will provide real opportunity to improve the treatment and outcomes for children with renal tumors on a global level.

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INTRODUCTION

The treatment of Wilms tumor (WT) has been one of the great success stories of modern medicine. Successive clinical trials conducted by the National Wilms Tumor Study Group (NWTSG), which was supplanted by the Children's Oncology Group (COG) in 2002, the International Society of Pediatric Oncology (SIOP), and other national study groups have resulted in overall survival (OS) rates exceeding 90%. Despite this remarkable achievement, the survival for certain patient subgroups, including those with unfavorable histologic and molecular features, bilateral disease, and recurrent disease remain well below 90%. Together, these higher risk groups compose 25% of patients with WT. Moreover, WT treatment comes at a cost, with nearly 25% of survivors reporting severe chronic health conditions, and this may be an underestimate because direct evaluation of survivors may detect conditions beyond those reported in questionnaires.[1,2] Although modern treatment regimens have reduced exposure to radiation therapy (XRT) and anthracyclines, two key culprits most associated with late effects, these agents remain mainstays of first-line treatment regimens. It is also critical to consider WT treatment advances from a global perspective, because survival in low-income countries greatly lags behind that of high-income countries.[3]

A key contributor to better patient outcomes has been refinement of therapy based on clinical and biologic risk factors. Until recently, only stage and histology were used to define treatment, but clinical trials now use a variety of clinical and biologic factors including patient age, tumor size and volume, response to chemotherapy, and loss of heterozygosity (LOH) at chromosomes 1p and 16q.[4,5] Although the stratification of WTs into risk-based subgroups has enabled clinicians to apply more precise therapy, it also has created the challenge of studying increasingly smaller subpopulations of patients. For instance, LOH at 1p/16q is a specific marker for increased risk of relapse in favorable-histology WT but occurs in approximately 5% of patients.[6] Likewise, some of the very high–risk WTs in need of novel therapies, such as anaplastic or postchemotherapy blastemal-type WT, compose only 10% to 15% of the overall population.[7-9] To enhance clinical trial design and feasibility leading to advancements in subsets of patients with rare cancer, there is

Table 1. Key Findings of Recent SIOP and NWTS/COG Renal Tumor Studies

Study	Key Findings
NWTS-5 (1995-2002)	With surgery only, 5-year RFS rate for stage I FH WT, age < 2 years, and tumor < 550 g was 84%, leading to early study closure; 5-year OS was 98%[10,11] Combined LOH at 1p and 16q predicted decreased RFS and OS for stage I-IV FH WT (2005)[6] RFS and OS inferior for stage I anaplastic WT compared with stage I FH WT[7] Best reported EFS and OS to date using VCR/DOX/CYCLO/ETOP for stage II-IV diffuse anaplastic WT[7]
COG AREN0321 (2006-2013)	VCR/irinotecan produced high response rate in a phase II study of newly diagnosed stage IV anaplastic WT[12] Patients with stage II-IV diffuse anaplastic WT treated with VCR/DOX/CYCLO/CARBO/ETOP (plus irinotecan for stage IV with phase II response) had EFS superior to NWTS-5, but with greater toxicity[13]
COG AREN0532 (2006-2013)	Re-evaluation of surgery only for stage I FH, age < 2 years, tumor < 550 g; results to be reported in 2015
COG AREN0533 (2007-2013)	Patients with stage IV FH WT with incomplete lung nodule response after 6 weeks of VCR/AMD/DOX showed superior EFS with the addition of CYCLO/ETOP compared with the estimated historical standard; results for patients with complete response treated without XRT will be reported in 2015 Results for patients with stage I-IV FH WT with combined LOH at 1p and 16q treated with additional chemotherapy will be reported in 2015
SIOP 93-01 (1993-1999)	Patients with stage I intermediate-risk WT did just as well with 4 weeks of postoperative VCR/AMD as with 18 weeks[14] Postchemotherapy histology predicted relapse, with inferior outcomes for patients with blastemal-type tumors[15] Lung XRT can be omitted from treatment of patients with stage IV WT if they have a complete response to chemotherapy and/or metastasectomy[16]
SIOP-2001 (2001-2012)	Stage I-III blastemal-type WT had superior EFS (and OS for stage I) compared with historical controls when treated with intensified chemotherapy[17] Stage II-III intermediate-risk WT did not have significant differences in EFS or OS when treated without doxorubicin[18] Stage IV WT with CT-only lung nodules had intermediate survival rates between those of children with normal CT scan of thorax and those with chest x-ray–detectable metastatic disease[19]

Abbreviations: AMD, dactinomycin; CARBO, carboplatin; COG, Children's Oncology Group; CT, computed tomography; CYCLO, cyclophosphamide; DOX, doxorubicin; EFS, event-free survival; ETOP, etoposide; FH, favorable histology; LOH, loss of heterozygosity; NWTS, National Wilms Tumor Study; OS, overall survival; RFS, recurrence-free survival; SIOP, International Society of Pediatric Oncology; WT, Wilms tumor; VCR, vincristine; XRT, radiation therapy.

a critical need for transcontinental international collaboration. Recognizing the importance of such collaboration, members of the COG Renal Tumor Committee (COG-RTC) and the SIOP Renal Tumor Study Group (SIOP-RTSG) have been meeting regularly for the past decade to share ideas and data, combine samples for biology studies, and inform each other's clinical trials. Conclusions from the most recent COG and SIOP studies are listed in Table 1.

OVERVIEW OF THE COG AND SIOP APPROACHES TO RENAL TUMORS

To understand the prospects and pitfalls of international collaboration for pediatric renal tumors, it is important to understand the differences in treatment approach and their implications. The COG-RTC advocates for up-front nephrectomy followed by chemotherapy. This approach allows for early and accurate histologic diagnosis, collection of biologic materials unaltered by therapy, and staging information before chemotherapy is administered, such as the presence of tumor spill or tumor involvement in lymph nodes. The SIOP-RTSG advocates for preoperative chemotherapy, which results in fewer tumor ruptures during surgery and lower postoperative stage.[20] The difference in timing of nephrectomy between COG and SIOP carries several repercussions for merging data and the conduct of joint clinical trials. First, prechemotherapy and postchemotherapy stage may have different connotations. For example, the clinical significance of local lymph node involvement among patients with stage III WT was evaluated in a joint study between COG-RTC and SIOP-RTSG. In the North American population, local lymph node involvement was the most important risk factor among patients with stage III disease and was twice as common as in the SIOP population, where local lymph node involvement was not predictive of outcome.[21,22] Seemingly similar patient subgroups may have different clinical outcomes depending on the treatment context.

There are also different implications of histology depending on whether the tumor is resected before or after chemotherapy is administered. The SIOP system assigns a histologic subtype and stratification based on histologic changes after chemotherapy.[9] Patients are divided into low-, intermediate-, and high-risk groups based on the degree of tumor necrosis and the relative proportion of each of the three cell types (epithelial, stromal, or blastemal) found in classical triphasic WT that remain in the viable component of the resected tumor after chemotherapy. These definitions are, by their nature, somewhat subjective.[23] Patients with diffuse anaplastic or blastemal-type WT after chemotherapy are classified as having high-risk histology. Recent data from the SIOP-2001 study indicate that augmentation of therapy for stage I blastemal-type WT improved survival, suggesting that this histologic classification system is clinically meaningful.[17] In the COG system of histologic categorization before chemotherapy, the blastemal content has less prognostic significance and is not independent of tumor stage.[24] The COG histologic classification system separates tumors into the following three broad categories based on the presence or absence of anaplasia: favorable histology (no anaplasia), focal anaplasia, or diffuse anaplasia.[24,25]

Summaries of WT treatment approaches on the most recently completed SIOP-2001 and COG AREN0321, AREN0532, and AREN0533 trials are provided in Tables 2 and 3. The tables nicely illustrate the complexity of comparing SIOP and COG results head to head. The intricacies of extrapolating results from the SIOP to the COG setting, and vice versa, are illustrated by considering the treatment of stage III WT. The SIOP-2001 study randomly assigned patients with stage III intermediate-risk WT to receive or not receive doxorubicin (DOX). The investigators dared to readdress this

Table 2. SIOP-2001 Treatment Approach

Stage	Preoperative Chemotherapy	Histology	Other Clinical or Biologic Factor	Postoperative Chemotherapy	XRT
I	AV × 4 weeks	Low risk		None	None
		Intermediate risk	Postoperative tumor volume > 500 mL*	AV × 4 weeks	None
		High risk		AVD × 27 weeks	None
II	AV × 4 weeks	Low risk		AV × 27 weeks	None
		Intermediate risk	Postoperative tumor volume > 500 mL*	AV × 27 weeks *v* AVD × 27 weeks	None
		High risk		DCBE × 34 weeks	25.2 Gy flank XRT; 10.8-Gy boost for lymph node involvement or gross disease
III	AV × 4 weeks	Low risk		AV × 27 weeks	None
		Intermediate risk	Postoperative tumor volume > 500 mL*	AV × 27 weeks *v* AVD × 27 weeks	14.4 Gy flank XRT; 10.8-Gy boost for lymph node involvement or gross disease
		High risk		DCBE × 34 weeks	25.2 Gy flank XRT; 10.8-Gy boost for lymph node involvement or gross disease
IV	AVD × 6 weeks	Low risk	Lung nodule CR†	AVD × 27 weeks	Flank XRT for local stage III‡
			No lung CR	DCBE × 34 weeks	15 Gy lung; flank XRT for local stage III‡
		Intermediate risk	Lung nodule CR†	AVD × 27 weeks	Flank XRT for local stage III‡
			No lung CR	DCBE × 34 weeks	15 Gy lung; flank XRT for local stage III‡
		High risk§	Lung nodule CR†	DCBE × 34 weeks	Flank XRT for local stage II/III‡
			No lung CR	DCBE × 34 weeks	15 Gy lung; flank XRT for local stage II/III‡

Abbreviations: AV, dactinomycin/vincristine; AVD, dactinomycin/vincristine/doxorubicin (cumulative doxorubicin dose, 250 mg/m^2 for stage I to III; 300 mg/m^2 for stage IV); CR, complete response; DCBE, doxorubicin/cyclophosphamide/carboplatin/etoposide (cumulative doxorubicin dose, 300 mg/m^2 for stage IV); SIOP, International Society of Pediatric Oncology; XRT, radiation therapy.
*In Germany, tumor volume > 500 mL after preoperative chemotherapy without stromal or epithelial predominance was assigned to high-risk histology.
†CR attained by chemotherapy or metastasectomy.
‡Metastatic sites other than lung were also irradiated; XRT dose varied according to metastatic site.
§Metastatic site irradiation regardless of response was mandated for anaplastic histology primary tumors and not if the abdominal tumor was blastemal type, unless anaplastic features were also found.

question, previously tested in the SIOP-6 and National Wilms Tumor Study (NWTS) -3 trials, because the newly defined high-risk postchemotherapy blastemal type subgroup was excluded from the random assignment and assigned to receive DOX. The study found that omission of DOX was not associated with inferior event-free survival (EFS) or OS, which will spare many patients the potential adverse effects of DOX exposure.[18] However, because there is no equivalent intermediate-risk group in the COG system, one cannot readily translate these findings to the COG treatment context. Moreover, patients with stage III tumors on the SIOP-2001 study received 14.4 Gy of flank or abdominal radiation, and patients received an additional 10.8 Gy to the para-aortic area if they had positive lymph nodes, bringing the total dose to 25.2 Gy for some patients. On the COG AREN0532 study, patients with stage III disease received 10.8 Gy regardless of lymph node involvement. It is unclear whether omission of DOX would result in acceptable EFS in the context of the lower radiation doses used in the COG system, although long-term follow-up of patients enrolled onto the NWTSG studies suggested that some patients treated without DOX had excellent OS.[26,27]

POTENTIAL SUBGROUPS FOR JOINT CLINICAL TRIALS

Notwithstanding the caveats discussed earlier, there are areas of commonality that would lend themselves to joint clinical trials. A retrospective analysis of 750 infants diagnosed with renal tumors before age 7 months was one of the first international clinical collaborative efforts. The study revealed that 34% of renal tumors in infants younger than age 7 months had histology other than WT, including congenital mesoblastic nephroma (18%), malignant rhabdoid tumor (8%), clear cell sarcoma of the kidney (2%), and other unspecified histologies (6%).[28] The high prevalence of renal tumors other than WT provided evidence to support immediate nephrectomy rather than preoperative chemotherapy in this age group, an exception to the usual SIOP practice in other age groups. Another collaborative effort led to treatment guidelines for patients at the opposite age spectrum—adolescents and adults with WT.[29] Adults with WT historically had inferior outcomes compared with children, but outcomes have improved when pediatric treatment regimens were followed. Challenges in treating adult WT include delayed diagnosis, lack of standardized treatment regimens, and intolerance of vincristine (VCR) -based therapy.[29] For the future, the following four high-priority patient groups have been identified for ongoing discussion and collaboration concerning treatment of WT: stage IV, initially inoperable, bilateral, and relapsed WT.

Stage IV WT

Patients with hematogenous metastatic disease to the lung, liver, or other sites are considered to have stage IV disease in both the SIOP and COG staging systems, regardless of local tumor stage. With the SIOP approach, patients with lung metastasis at diagnosis are treated with 6 weeks of VCR/dactinomycin (AMD)/DOX chemotherapy before nephrectomy.[16,30] If the lung nodules respond completely to chemotherapy or are completely surgically resected, patients do not receive lung XRT. Chemotherapy after the initial 6 weeks is based on histologic findings; the majority of patients with intermediate-risk disease continue three-drug chemotherapy with a cumulative DOX

Table 3. COG AREN0321, AREN0532, and AREN0533 Treatment Approach

Stage	Histology	Other Clinical or Biologic Factor	LOH 1p and 16q	Chemotherapy	XRT
I	Favorable	Age < 2 years and tumor < 550 g	Any	None	None
		Age ≥ 2 years or tumor ≥ 550 g	No	AV × 19 weeks	None
		Age ≥ 2 years or tumor ≥ 550 g	Yes	AVD × 25 weeks	None
	Focal anaplasia	Any	Any	AVD × 25 weeks	10.8 Gy flank
	Diffuse anaplasia	Any	Any	AVD × 25 weeks	10.8 Gy flank
II	Favorable	Any	No	AV × 19 weeks	None
			Yes	AVD × 25 weeks	None
	Focal anaplasia	Any	Any	AVD × 25 weeks	10.8 Gy flank
	Diffuse anaplasia	Any	Any	VDCBE × 30 weeks	10.8 Gy flank
III	Favorable	Any	No	AVD × 25 weeks	10.8 Gy flank/abdomen; 10.8-Gy boost for gross disease
			Yes	VDACE × 31 weeks	
	Focal anaplasia	Any	Any	AVD × 25 weeks	10.8 Gy flank/abdomen; 10.8-Gy boost for gross disease
	Diffuse anaplasia	Any	Any	VDCBE × 30 weeks	20 Gy flank/abdomen; 10.8-Gy boost for gross disease
IV	Favorable	Week 6 lung nodule CR	No	AVD × 25 weeks	No lung XRT
		Week 6 lung nodule CR	Yes	VDACE × 31 weeks	12 Gy lung*
		Week 6 lung nodule no CR	Any	VDACE × 31 weeks	12 Gy lung*
	Focal anaplasia	Any	Any	VDCBE × 30 weeks	12 Gy lung*
	Diffuse anaplasia	Any	Any	VDCBEI × 36 weeks†	12 Gy lung*

Abbreviations: AV, dactinomycin/vincristine; AVD, dactinomycin/vincristine/doxorubicin (cumulative doxorubicin dose, 150 mg/m^2); COG, Children's Oncology Group; CR, complete response; VDACE, vincristine/doxorubicin/dactinomycin/cyclophosphamide/etoposide (cumulative doxorubicin dose, 195 mg/m^2); VDCBE, vincristine/doxorubicin/carboplatin/cyclophosphamide/etoposide; VDCBEI, vincristine/doxorubicin/carboplatin/cyclophosphamide/etoposide/irinotecan (cumulative doxorubicin, dose 225 mg/m^2); XRT, radiation therapy.

*Metastatic sites other than lung were also irradiated; XRT dose varied according to metastatic site.

†Patients with stage IV disease received vincristine/irinotecan only if a response was seen after 6 weeks of phase II window therapy.

dosage of 300 mg/m^2. Historically, patients on NWTSG studies with lung metastases received lung XRT, regardless of lung nodule response.[31] On the basis of findings from SIOP that survival correlates with completeness of lung nodule response,[30] the recently completed COG AREN0533 study adapted therapy according to lung nodule response. All patients initially received 6 weeks of treatment with VCR/AMD/DOX. If the lung nodules responded completely, patients continued the same chemotherapy with a cumulative DOX dose of 150 mg/m^2 and lung XRT was omitted. If the lung nodules did not respond completely, biopsy was encouraged to assess histology. If the lung nodule(s) were confirmed to be tumor or if they were not biopsied, cyclophosphamide/etoposide was added to the chemotherapy regimen and patients received lung XRT. The preliminary results suggest that this augmentation of therapy improved outcomes for patients with incomplete lung nodule response compared with the expected EFS in that patient group.[32] Results for the group of patients with complete lung nodule response who did not receive lung XRT will be presented in 2015.

The avoidance of lung XRT in select patients with stage IV WT represents a convergence of treatment approach between COG and SIOP. Both groups also face the same challenge of standardizing definitions of clinically significant metastatic disease at diagnosis and adequate response to chemotherapy to avoid XRT in the era of high-resolution computed tomography scanning.[19,33] The COG AREN03B2 Renal Tumor Biology and Classification Study incorporates central radiology review of computed tomography scans to detect pulmonary nodules. A patient is considered to have metastatic disease if a round, noncalcified nodule that is not in one of the pulmonary fissures is detected. This definition is imperfect because other studies have shown that when biopsied, only approximately 75% of small lung nodules are proven to be WT.[34] Moreover, inter-reader variability among radiologists in the detection of lung nodules has been documented.[35] Although biopsy remains the gold standard of defining the histology of lung nodules, in many cases, biopsy is not feasible because of the size, number, and location of the nodules and/or patient clinical status. Despite its limitations, the consistent COG central radiology review process offers a standardized definition of metastatic disease and provides a starting point for improved understanding of the management of pulmonary nodules. The new SIOP Umbrella protocol, opening in 2015, aims to introduce centralized radiology review across Europe for the first time.

Initially Inoperable WT

Although most patients on COG studies undergo immediate nephrectomy, COG guidelines indicate that certain patients should be considered for preoperative chemotherapy, including those with extension of inferior vena cava tumor thrombus above the level of the hepatic veins, tumor involving contiguous organs whereby the only means of removing the kidney tumor requires removal of the other organ, and tumors for which the surgeons' judgment is that nephrectomy would result in significant or unnecessary morbidity/mortality, tumor spill, or residual tumor.[36] In the COG system, tumors that do not undergo immediate resection are considered local stage III by definition and are treated with flank or abdominal XRT. In the SIOP system, there is no surgical decision about the possibility of immediate nephrectomy because stage is determined after preoperative chemotherapy is administered. Only patients who have stage III disease for reasons such as positive lymph nodes, positive surgical margins, tumor rupture, or peritoneal implants receive flank or abdominal XRT.

Approximately 20% of patients with overall stage III disease and 40% of patients with overall stage IV disease underwent delayed nephrectomy on the recently completed COG AREN0532 and AREN0533 studies. The sizable number of patients receiving preoperative chemotherapy raises the question of whether the SIOP approach to tailoring therapy based on postchemotherapy histology should be applied in the COG protocols, allowing reduction in therapy (XRT and DOX) for patients who have local stage III disease solely on the basis of preoperative chemotherapy. Conversely, patients receiving preoperative therapy may inform whether prognostic biomarkers defined in COG studies should be used in SIOP protocols. This patient subgroup lends itself well to pooled analyses between the international groups.

Bilateral WT

Stage V (bilateral) disease is also treated similarly in the COG and SIOP protocols. In either system, patients undergo preoperative chemotherapy to shrink the tumors and facilitate nephron-sparing surgery. The recently completed COG AREN0534 study treated patients with bilateral WT with VCR/AMD/DOX therapy for the first 6 to 12 weeks of treatment to optimize tumor shrinkage and potential for nephron-sparing surgery. The rationale for using DOX was that Paulino et al[37] found that a three-drug regimen including VCR/AMD/DOX resulted in a significantly lower relapse rate (8%) compared with VCR/AMD (42%) in patients with synchronous bilateral WT. In addition, on NWTS-4 and NWTS-5, the EFS for synchronous bilateral WT of favorable histology was only 65% to 75%, suggesting that patients with bilateral WT may benefit from additional therapy to reduce the risk of relapse.[6,38] The SIOP-2001 study advocated for initial treatment with just VCR/AMD, with the idea that DOX could be added at a later time if the response to two-drug therapy was inadequate. Whether the addition of DOX up front increases the percentage of patients undergoing partial rather than complete nephrectomy or impacts EFS and OS remains to be determined. Of note, AREN0534 is the first COG study to adopt the SIOP histologic classification system to guide postoperative chemotherapy. The parallel approach to treating bilateral WT provides opportunity for joint analysis and expediting advances, perhaps via the future conduct of a single study for bilateral disease.

Relapsed WT

The survival rate for recurrent WT historically was only 25%, although newer treatment regimens containing additional effective chemotherapy agents have greatly improved outcomes.[39-44] A collaborative review conducted between SIOP and COG suggested that patients with relapsed WT may be divided into risk groups according to survival rates after salvage therapy.[45] The standard-risk group includes patients with nonanaplastic WT with relapse after primary therapy including at most two drugs, typically VCR and AMD. Such patients are expected to have a survival rate of 70% to 80%.[41] The high-risk group includes patients with nonanaplastic WT with relapse after primary therapy including three or more agents, typically VCR, AMD, DOX, and XRT. These patients are expected to have a survival rate of 40% to 50%.[42] The very high–risk group includes patients with recurrent anaplastic or blastemal-type WT. These patients are expected to have survival rates of only 10%.[7,43]

The value of high-dose therapy with stem-cell transplantation (HDSCT) for the treatment of recurrent WT is one of the unsettled questions in the field. Several groups have reported improved outcomes with HDSCT, with EFS estimates ranging from 36% to 60%,[46-50] yet other groups have reported similar outcomes with conventional doses of chemotherapy.[39] A prospective clinical trial to randomly assign patients to receive or not receive HDSCT was proposed by the COG-RTC and SIOP-RTSG almost a decade ago, but the study was disapproved by regulatory and funding agencies because of concerns about a protracted study duration (estimated at 8 years), scarcity of funding, and anticipation that HDSCT would not yield a major benefit. An international meta-analysis conducted to provide additional insights revealed that the patients most likely to benefit from HDSCT were those initially treated with four or more chemotherapeutic agents and those with multiple relapses or progression on salvage therapy.[51] Although imperfect, the meta-analysis provides the best guidance for when HDSCT should be considered.

Although attempts to conduct an international trial to evaluate the benefit of HDSCT were unsuccessful as a result of resource limitations, there remains keen interest in international collaboration to improve outcomes for recurrent WT. Because primary treatment and risk groups differ between SIOP and COG, the two groups are actively discussing how to define and harmonize relapse risk groups. For the patients at lowest risk, conventional chemotherapy enhancements such as adding camptothecins to more traditional chemotherapy backbones can be tested to improve salvage efficacy. Given the relative rarity of higher risk recurrent WTs, jointly conducted clinical trials could evaluate the efficacy of novel agents using either traditional or randomized phase II designs possibly integrating Bayesian approaches.

BIOLOGIC INSIGHTS FROM INTERNATIONAL COLLABORATION

Continued improvements in WT therapy are likely to be achieved through a more complete understanding of tumor biology. Biology studies may allow for more precise risk-adapted therapy based on molecular prognostic markers and identify novel therapeutic targets with a more favorable efficacy/toxicity profile compared with standard chemotherapeutics. The COG-RTC and SIOP-RTSG have been holding International Conferences on Pediatric Renal Tumor Biology every 2 to 5 years starting in 1992; the eighth conference was held in Bethesda, Maryland, in 2013. Review of select conference abstracts over time demonstrates the remarkable expansion of knowledge achieved over two decades (Appendix Table A1, online only). We anticipate that the next meeting, planned for 2016, will feature results of integrative "omic" analysis of WT including emerging data from exome and whole-genome sequencing, methylome, miRNA expression, copy number changes, and RNA expression platforms.

The following sections describe recent biologic observations that are likely to impact WT therapy. Each of these findings involved international collaboration that entailed exchange of biologic samples, discussion of study design, or corroboration of one group's findings using an independent study set.

Loss of Heterozygosity of 1p and 16q

In 1992, frequent LOH of chromosome 16q was identified in WT, sometimes in conjunction with LOH at chromosome 1p.[52] A subsequent study evaluating patients enrolled onto NWTS-3 and

NWTS-4 found LOH at either 1p or 16q to correlate with adverse prognosis.[53] The association of 16q LOH and adverse prognosis was confirmed by studies from the United Kingdom and Germany.[54-56] Building on this background, NWTS-5 prospectively evaluated the prognostic significance of 1p and 16q LOH in more than 1,700 patients with favorable-histology WT. LOH at either 1p or 16q showed trends toward increased risks of relapse or death, but the greatest effect was seen with combined LOH at both loci, found in approximately 5% of favorable histology WTs.[6] On the basis of these findings, the recently closed COG AREN0532 and AREN0533 studies augmented therapy for patients with combined LOH at both 1p and 16q; results of these therapeutic interventions will be reported in 2015.

The prognostic significance of 1p and 16q LOH was also evaluated in 426 patients enrolled onto the United Kingdom WT 1 to 3 Studies. The proportion of patients with 1p and 16q LOH was similar to the NWTS study, but only 2% (v 5% in the NWTS study) had combined LOH at both loci.[51] LOH at 16q was associated with higher risk of relapse or death compared with no LOH, but no association was seen with 1p. A meta-analysis combining data from the United Kingdom WT 1 to 3 Studies and NWTS-5 indicated that LOH at either locus had an independent effect on prognosis that was multiplicative when combined.[57] The Italian Cooperative Group also reported on the negative effect of 1p loss but not for other chromosomal regions tested, including 16q.[58]

LOH analysis of tumors treated within the SIOP trial in Germany has also confirmed the adverse prognostic impact several loci (16q, 11q, and 22q), but these changes were associated with high-risk histologic features and, hence, not independent adverse prognostic factors.[55,56] For this reason, the SIOP group does not yet use molecular biomarkers for risk stratification, but instead takes advantage of the in vivo histologic response of each child's tumor to identify a category of blastemal-type Wilms tumor, which is by definition chemotherapy resistant and high risk.

Chromosome 1q Gain

Gain of chromosome 1q is one of the more common cytogenetic abnormalities observed in WT, occurring in approximately 30% of tumor samples.[59] Retrospective studies conducted in the United Kingdom demonstrated an association between 1q gain and tumor recurrence.[60-63] Interestingly, an association between 1q gain and loss of chromosomes 1p and 16q was noted, indicating that the prognostic significance of LOH at 1p and 16q may not be independent of 1q gain.[64] A more expansive analysis of 331 patients treated at centers in the Children's Cancer and Leukemia Group of the United Kingdom confirmed that 1q gain was associated with inferior EFS and OS.[65] An analysis of 212 patients treated on NWTS-4 observed 8-year EFS of 76% for patients with 1q gain versus 93% for those lacking 1q gain ($P = .0024$).[66] Eight-year OS was 89% (95% CI, 78% to 95%) with 1q gain versus 98% (95% CI, 94% to 99%) without 1q gain ($P = .0075$). Both COG and SIOP are about to report on the prognostic significance of gain of 1q in much larger numbers of patients with WT treated with either immediate nephrectomy in the NWTS-5 trial or with preoperative chemotherapy in the SIOP WT 2001 trial. Future COG studies will likely incorporate 1q gain into the risk stratification schema for favorable-histology WT. Its value as an independent prognostic factor alongside histologic response to chemotherapy is under evaluation and will be tested in the new SIOP Umbrella study, as will intratumoral heterogeneity of copy number changes.

Genetic Analysis of Anaplastic WT

The presence of anaplastic histology is perhaps the most powerful adverse prognostic feature for WT.[7] Several lines of evidence suggest that anaplastic WT arises from the acquisition of a *TP53* mutation in a tumor of favorable histology.[67] First, the distribution of anaplasia within a WT sample can be focal, with *TP53* mutations or protein overexpression restricted to areas of anaplasia.[25,68] Second, patients with bilateral WT often have discordant histologies between contralateral tumors, suggesting that the underlying genetic driver is distinct from the molecular driver of anaplasia.[7] Third, some WTs have favorable histologic features at diagnosis but are found to have anaplastic histology at relapse, suggesting clonal evolution.[69] A recent study from the United Kingdom, which included samples provided by the COG, assessed *TP53* mutational status in 40 patients with diffuse anaplastic WT. Patents with tumors with *TP53* mutations and/or 17p loss (the locus of *TP53*) had an increased risk of recurrence and death compared with patients with tumors lacking *TP53* alterations. A larger genomic analysis of diffuse anaplastic WT is under way by COG investigators and is expected to be reported in 2015. Recent studies also have identified a significant association between *MYCN* amplification and anaplastic histology, with approximately 30% of anaplastic tumors having *MYCN* amplification.[70-72] Moreover, *MYCN* amplification was associated with inferior EFS and OS, independent of histology.

MicroRNA-Processing Gene Mutations in WT

Several groups recently found that approximately 15% of WT have microRNA (miRNA) -processing gene mutations. A Brazilian group, using samples provided by the COG, found *DROSHA* mutations in 12% of samples evaluated.[73,74] Other miRNA-processing genes including *DGCR8*, *DICER1*, *XPO5*, *TARBP2*, and *DISL32* were mutated in WT at lower frequencies.[73,74] These results were corroborated in a smaller single-institution study, which in addition demonstrated that miRNA gene mutations impair the expression of tumor-suppressing miRNAs including the let-7 family, which is involved in renal tumor development.[75] Two other studies published as companion articles, one from the COG and one from the SIOP/Gesellschaft fur Padiatrische Onkologie und Hamatologie, confirmed the relatively high frequency of miRNA-processing gene mutations in WT and found that such mutations often occur concurrently with mutations of *SIX1* and *SIX2*, which encode transcription factors critical to the mesenchymal-to-epithelial transition in embryonic renal development.[74,76,77]

SUMMARY AND FUTURE DIRECTIONS

It is a propitious time for WT research because clinical outcomes are at an all-time high and there is unprecedented understanding of tumor biology. Nevertheless, 25% of patients with WT have predicted survival estimates well below the overall 90% benchmark and 25% of survivors of WT report severe or life-threatening chronic health conditions. The identification of clinical and biologic prognostic markers, such as persistence of blastemal cells after chemotherapy and LOH of chromosomes 1p and 16q, has enabled more precise delivery of therapy. However, improved risk stratification has divided the population

of patients with WT into small subgroups, creating the challenge of designing and executing clinical trials that are sufficiently powered to demonstrate the desired outcomes. Surmounting this challenge will require enhanced collaboration between the COG-RTC, the SIOP-RTSG, and other national WT study groups. The fruits of stepped-up international collaboration are beginning to be realized, with the discovery of new genes, biologic markers, and therapeutic targets. Moreover, the COG-RTC and SIOP-RTSG have increasingly been applying lessons learned from each other's studies to their own treatment algorithms. Although this article focused on WT, international collaboration also will inform treatment of less common pediatric renal tumors such as malignant rhabdoid tumor, clear cell sarcoma, and renal cell carcinoma. The benefits of COG-SIOP collaboration will hopefully translate into application of evidence-based diagnostic and therapeutic approaches in low-income countries. The international community of WT researchers is committed to continuing joint efforts to improve the treatment and outcomes for children with renal tumors on a global level.

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Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration

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Appendix

Table A1. International Pediatric Renal Tumor Biology Conferences

Meeting	Location and Year	Major Themes
1	Albuquerque, NM, 1992	Tumor banking; first 120 cases in Pediatric Oncology Group Tumor Bank Cytogenetic changes in Wilms tumor Early studies of loss of heterozygosity at 11p, 1p, and 16q *WT1* expression and correlation with histology
2	Philadelphia, PA, 1995	*WT1* mutations in bilateral Wilms tumor 11p15 alterations in Wilms tumor and Beckwith-Wiedemann syndrome Cytogenetic changes in Wilms tumor
3	Philadelphia, PA, 1997	*FWT1* as a familial Wilms tumor locus Large-scale studies of LOH 1p and 16q as a prognostic marker
4	London, United Kingdom, 2002	*WT1*-based immunotherapy Early studies of gene expression profiles in Wilms tumor New genes/loci in Wilms tumor: *HACE1*, chromosome 7p
5	Vancouver, British Columbia, Canada, 2005	Array comparative genomic hybridization (CGH) and more gene expression profiles
6	Chamonix, France, 2008	New genes/loci: *WTX* Interactions between *WT1*, *CTNNB1*, and *WTX* in Wilms tumorigenesis Animal models: mice, zebrafish, rats Novel therapeutic targets: Stat pathway, IGF
7	Banff, Alberta, Canada, 2010	*WT1* in Wilms tumor development: collaboration with Wnt signaling, Igf2 Association between 1q gain, 1p loss, 16q loss, and relapse New genes in Wilms tumor: *FBXW7, MYCN* Novel therapeutic targets: MTOR pathway, telomerase, IGF
8	Bethesda, MD, 2013	Wilms tumor stem cells; CD56 as a therapeutic target Large-scale studies confirming 1q gain as a prognostic factor Aneuploidy and *TP53* mutations in anaplastic Wilms tumor *DICER1* mutations in renal tumors and deregulation of microRNA Novel therapeutic targets: results from Pediatric Pre-Clinical Testing Program Urine and serum proteomics Biology of pediatric renal cell carcinoma

Abbreviation: IGF, insulin-like growth factor.