Original Article

Synchronous Bilateral Wilms Tumor

A Report from the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)

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BACKGROUND: The optimal management of bilateral Wilms tumor (BWT) is challenging, and their survival is lower than for unilateral tumors. This report discusses a large series of BWTs treated in Italy in the last 2 decades. **METHODS:** This analysis concerns patients with synchronous BWT registered at Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) centers between 1990 and 2011; details on their treatment and outcome are presented and discussed. **RESULTS:** Ninety BWTs were registered in the AIEOP Wilms tumor database. Preoperative chemotherapy was given for a median 12 weeks before definitive tumor resection was attempted. Forty-eight percent of the patients had preservation of bilateral renal parenchyma. The proportion of bilateral nephron-sparing surgeries was not higher in the 37 patients initially given doxorubicin/vincristine/actinomycin D (32%) than in the 43 children receiving vincristine/actinomycin D alone (58%). The 4-year disease-free survival rate was 66.5% ± 5% and overall survival was 80% ± 5% for the cohort as a whole. The 4-year disease-free survival (overall survival) for 18 children with diffuse anaplasia or postchemotherapy blastemal-type tumors was 51% ± 13% (62% ± 13%), as opposed to 72% ± 3% (88% ± 4%) for 68 children with a favorable histology (log-rank $P = .04$ [$P = .007$]). **CONCLUSIONS:** These results provide further evidence that the optimal duration and choice of drugs for preoperative chemotherapy remain an open question. Outcome remained significantly worse for BWT than for unilateral Wilms tumor. To enable the conservative treatment of as many affected kidneys as possible, only centers with experience in BWT should manage such cases. ***Cancer*** **2013;000:000–000.** © *2013 American Cancer Society.*

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The long-term disease-free survival (DFS) rate for patients with localized Wilms tumor (WT) is now approaching 90%, and approximately 70% for those with metastatic disease.[1,2] This excellent outcome is the result of collaborative efforts by different specialists in national or international cooperative studies. WT may present with bilateral synchronous kidney involvement in 5% to 7% of affected children,[3] and their DFS (in the range of 60%-70%) is not as good as that for unilateral WT[4]; furthermore, the risk of end-stage renal disease remains high in this subgroup of patients.[5] Bilateral WT (BWT) is likely to be associated with the presence of nephrogenic rests, congenital malformations, or predisposing syndromes as well.[3,6] A major challenge in BWT management is to achieve cure rates as high as in unilateral cases while preserving a renal function sufficient for normal growth and development.

The 2 largest cooperative groups devoted to studying the optimal approach to treatment for WT—the National WT Study (NWTS) group and the International Society of Pediatric Oncology (SIOP)—have never designed a formal trial

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focusing on BWT, but rather have merely suggested treatment guidelines. Only recently, the protocol designed by the Children's Oncology Group (COG), which is the successor of the NWTS group, has included a prospective branch dedicated to children with bilateral disease (named AREN0534).[7] While we wait for this study to be completed, the lack of any specific protocol for managing BWT will continue to give rise to a great variability in its treatment, although partly because of the heterogeneity of the disease itself and patients' different response to preoperative chemotherapy, which calls for a tailored approach in most cases.

To shed more light on BWT, we retrospectively reviewed and analyzed the characteristics and outcome of treatment in children with BWT treated in Italy over the past 20 years.

MATERIALS AND METHODS

Querying the WT database of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) identified 93 cases of synchronous bilateral renal disease (diagnosed at 18 AIEOP centers) among 1413 registered cases of WT (corresponding to 6.6% of the total sample enrolled in the database) collected from August 1990 to May 2011.

All patients were treated according to the guidelines for BWT given in the protocols applied at the time. The treatment protocols had been approved by the participating institutions' review boards, and specific informed consent was obtained from the parents.

Treatment Guidelines

The core strategy of the guidelines across all the protocols involved preoperative chemotherapy, based on weekly vincristine (V) injections, plus actinomycin D (A) every 2 weeks, for a 4-week treatment block, to be repeated (1 to 3 times), aiming for the maximum tumor shrinkage before the feasibility of definitive resection was evaluated. Doxorubicin (D) was added to the 2-drug VA regimen in cases presenting with metastases or evidence of venous tumor thrombi on baseline imaging. Postoperative therapy followed the recommendations for unilateral tumors, depending on the tumor's stage and histology: chemotherapy for stages I and II included VA for approximately 6 months; therapy for stage III consisted of the VAD regimen plus radiotherapy (to the flank or whole abdomen, depending on tumor extent or abdominal contamination) for 8 months. Cases presenting with diffuse anaplasia or (in more recent years) with postchemotherapy blastemal-type histology received an intensified chemotherapy regimen, including additional agents such as either ifosfamide or cyclophosphamide, along with carboplatin and etoposide.

TABLE 1. Patient and Treatment Characteristics

Characteristic	No. (%)
Sex	
Male	32 (34%)
Female	61 (66%)
Total	93
Histology	
Nephroblastomatosis	3 (3%)
Favorable histology Wilms tumor	67 (76%)
Unfavorable histology Wilms tumor	18 (21%)
Total	88
Genetic malformations/syndromes	
Beckwith-Wiedemann syndrome	3
WAGR syndrome	2
Perlman syndrome	1
Denys-Drash syndrome	1
Prune belly syndrome	1
Isolated hemi-hypertrophy	5
Isolated aniridia	2
Mental and growth retardation	1
Metastases	
Yes	11 (12%)
No	79 (88%)
Total	90
Preoperative treatment	
Regimen VA	43 (49%)
Regimen VAD	37 (43%)
Other drugs	1 (1%)
None	6 (7%)
Total	87
Type of surgery	
RN with contralateral NSS	31 (35%)
RN with contralateral needle biopsy/inspection	12 (14%)
Bilateral NSS	35 (40%)
Unilateral NSS with contralateral only inspection	5 (6%)
Bilateral biopsies	1 (1%)
Bilateral nephrectomy	1 (1%)
No surgery	3 (3%)
Total	88
Radiotherapy	
No	62 (76%)
Yes	20 (24%)
Total	82

Abbreviations: NSS, nephron-sparing surgery; RN, radical nephrectomy; V, vincristine; A, actinomycin; D, doxorubicin; WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.

A retrospective review of the hospital records, surgical records, pathology findings, and treatment details were retrieved from the charts.

Statistical Analysis

Overall survival (OS) was defined as the time from diagnosis to death due to any cause. Disease-free survival (DFS) was calculated from diagnosis to the first occurrence of tumor recurrence or progression. OS and DFS were calculated using the Kaplan-Meier method[8]; comparisons between probabilities in different patient groups were drawn using the log-rank test. All *P* values were 2-

sided, and values below .05 were considered statistically significant. Associations between certain treatment characteristics, eg, the addition of doxorubicin (the VAD regimen versus VA) and surgical outcome (bilateral nephron-sparing surgery versus at least 1-sided radical nephrectomy), were tested with Fisher's exact test. The statistical analysis was performed using StatView software (version 5.0.1, SAS Institute Inc.).

RESULTS

A total of 93 children with synchronous bilateral disease were registered. The female/male ratio was 1.9, and the children's median age at diagnosis was 24 months (range, 5-86 months). Forty patients underwent initial biopsy (using an 18-gauge needle in most cases). Three children were eventually ruled out because they had bilateral nephroblastomatosis alone, with no histological evidence of WT, whereas 3 children with WT arising in a previously identified nephroblastomatosis were included in the final group of 90 cases of BWT forming the object of the present analysis. Table 1 summarizes the general characteristics of the whole cohort of patients.

Of 11 children with metastatic disease at diagnosis, 9 had lung metastases and 2 had liver metastases. Associated congenital syndromes or genitourinary anomalies were noted in 16 patients (18%).

Preoperative Treatment

The initial chemotherapy regimen adopted was VA for 43 patients, whereas 37 were treated with the VAD regimen (including 11 children with metastatic disease); only 1 patient received additional drugs (ifosfamide/carboplatin). Although preoperative chemotherapy was recommended, 6 children were managed with primary resection. In 3 other cases, the type of preoperative chemotherapy was not known.

The duration of preoperative chemotherapy (ie, time elapsing between starting chemotherapy and first surgical resection) varied considerably, ranging between 1 and 40 weeks (median, 12 weeks).

Surgery

A total of 43 of 85 patients whose surgical reports were available underwent unilateral radical nephrectomy with either contralateral nephron-sparing surgery (NSS) (31 cases), or biopsy (8 cases), or inspection alone (4 cases). Forty-one patients underwent conservative surgical management bilaterally: 35 had bilateral NSS; 5 had only unilateral NSS and exploration of the other kidney; and 1 only had bilateral biopsies. Bilateral radical nephrectomy was unavoidable in 1 patient. Three children never had any definitive surgery, due to early septic death in 1 case and to physicians' or parents' decisions in 2 cases of early tumor progression. Overall, 45 of 176 kidneys (26%) were totally removed, and 41 of 85 patients (48%) who underwent definitive surgery were finally managed with conservative surgery. Nineteen patients underwent 2 separate surgical procedures to achieve definitive surgical tumor removal. No data were available on 2 patients.

Two patients died as a result of surgical complications (an inadequately treated chylous ascites in one case, due partly to the parents refusing exploratory second-look surgery; and a likely acute cerebral ischemia after bilateral radical nephrectomy, which eventually proved necessary due to multiple refractory relapsing bilateral tumors, in the other). Other reported major perioperative complications included 1 case of urinary fistula, 1 case of splenic injury (necessitating splenectomy), and 1 case of bowel obstruction (requiring repeat laparotomy).

The proportion of definitive bilateral NSS was not higher among the 37 children initially given more than 2 drugs (of whom 12 cases had NSS) than among the 43 children initially treated with VA (NSS = 25) (Fisher's exact $P = .03$).

TABLE 2. Characteristics of Patients With Recurrent/Progressive Disease

Characteristic	No. (%)
Sex	
Male	14 (45%)
Female	17 (55%)
Histology	
Favorable histology Wilms tumor	19 (65%)
Unfavorable histology Wilms tumor	10 (35%)
Not known	2
Metastases at diagnosis	
Yes	5 (16%)
Preoperative treatment received	
Regimen VA	18 (67%)
Regimen VAD	9 (33%)
Not known	4
Type of surgery	
RN with contralateral NSS	11 (39%)
RN with contralateral needle biopsy/inspection	3 (11%)
Bilateral NSS	12 (43%)
Unilateral NSS with contralateral only inspection	2 (7%)
Not known	3
Sites of tumor recurrence[a]	
Local	17 (68%)
Metastatic	5 (20%)
Combined	3 (12%)
Not known	2

[a] Excluding the 4 cases suffering from primary tumor progression.Abbreviations: V, vincristine; A, actinomycin; D, doxorubicin; NSS, nephron-sparing surgery; RN, radical nephrectomy.

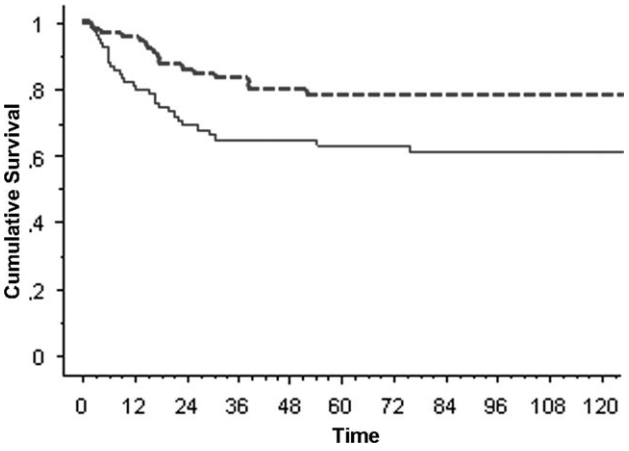

Figure 1. Kaplan-Meier estimates are shown for 4-year disease-free survival (66.5% ± 5%) (solid line) and overall survival (80% ± 5%) (dashed line) rates for 90 children with bilateral synchronous Wilms tumor (elapsed time is expressed in months).

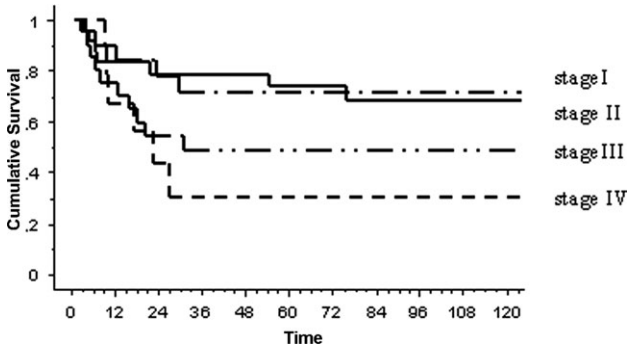

Figure 2. Kaplan-Meier estimates are shown for 4-year disease-free survival rate according to "local" tumor stage: 76% ± 9% for stage I; 74% ± 10% for stage II; 53% ± 11% for stage III; 36% ± 16% for stage IV (P = .12) (elapsed time is expressed in months).

Histology

Final pathology was not available for 5 patients (3 never underwent surgery or biopsy, whereas the pathologist's report was missing in 2 cases). Diffuse anaplasia in at least 1 kidney, never presenting with metastatic disease, was diagnosed in 10 of 85 cases (12%), and a blastemal-type histology according to the SIOP classification in 8 of 85 cases (9%), one with metastatic disease at the baseline.

Local tumor staging was done at the time of surgical exploration in 79 patients, based on the highest local tumor stage attributable to either of the 2 kidneys: 25 cases (30%) were stage I, 26 cases (35%) were stage II, and 28 cases (30%) were stage III. Local staging was not done in 11 cases due to a shortage of data or because no definitive surgery was ever performed.

Radiotherapy

Radiotherapy was administered to 20 children (no data were available on 8 cases): to the whole abdomen in 9 cases and to one flank in 9 cases (at doses ranging from 10-14 Gy); and to the tumor bed alone in 2 cases (one given 10 and the other 20 Gy). In 14 cases, the flank/abdomen were irradiated due to local stage III tumor (including 4 cases with unfavorable histology), whereas for the other 6 cases, the indications for radiation therapy were not stated. It is noteworthy that 12 of 28 patients classified as having local stage III tumors received no local radiotherapy at the discretion of the local physician. Two of the 9 patients displaying lung metastases at diagnosis underwent whole-lung radiotherapy as part of their initial treatment, whereas 7 patients received no radiotherapy, due mainly to the complete remission of their lung nodules after primary chemotherapy.

Outcome

The disease recurred or progressed in 27 and 4 children, respectively, a median 12 months after the initial diagnosis (range, 2-139 months). The sites of relapse were as follows: local alone in 17 cases, metastatic in 5 cases (4 to the lung, 1 to the liver); and combined in 3 cases (local plus lung and liver); the site of relapse was not stated in 2 cases. Table 2 shows the characteristics of the relapsing patients, 10 of whom had an unfavorable histology at initial diagnosis (diffuse anaplasia in 2 cases, blastemal-type in 8 cases). Overall, 17 children died: 12 because of their tumor and 5 due to toxicity (sepsis in 2 cases, veno-occlusive disease in 1 case, and perioperative complications in 2 cases).

After a median follow-up of 93 months (range, 13-222 months), the 4-year DFS and OS rates were 66.5% ± 5% and 80% ± 5%, respectively, for the cohort as a whole (Fig. 1). The 4-year DFS (OS) according to "local" tumor stage was as follows: 76% ± 9% (92% ± 5%) for stage I; 74% ± 10% (79% ± 10%) for stage II; 53% ± 11% (76% ± 10%) for stage III; and 36% ± 16% (67% ± 16%) for stage IV (P = .12 [P = .39]) (Fig. 2).

Eighteen children with diffuse anaplasia or postchemotherapy blastemal-type tumors had a 4-year DFS (OS) rate of 51% ± 13% (62% ± 13%), as opposed to 72% ± 3% (88% ± 4%) in the 67 children with a favorable histology (log-rank P = .04 [P = .007]). The DFS did not differ significantly between patients treated with bilateral NSS (72% ± 7%; N = 41) and those who had radical nephrectomy for at least 1 kidney (64% ± 8%; N = 44) (P = .9).

To discuss the possible effect on survival of adding doxorubicin, only nonmetastatic patients were compared;

there was a trend toward a better DFS in 28 nonmetastatic patients treated with VAD (83% ± 8%) versus 42 patients treated with VA (65% ± 7%), but this was not statistically significant ($P = .16$).

DISCUSSION

Treatment guidelines for children with BWT have been provided in several protocols, but these patients have never been the object of a dedicated formal study, nor have they ever been randomized for specific treatment. This shortcoming is partially due to the heterogeneous nature of bilateral tumors, which require tailored treatment decisions in the majority of cases, making a standardized approach very difficult.

Our study on 90 children with BWT focused on shedding further light on the clinical characteristics, treatment, and outcome of this rare condition, although we are fully aware that the significant inter- and intra-institutional management variability may preclude any generalizations.

Our DFS and OS rates of 64% and 78%, respectively, were comparable with those of other, single- or multicenter experiences.[4,9-15] Factors that may contribute to this worse outcome include understaging, incomplete tumor resection, a higher incidence of anaplasia, and a genetic predisposition to WT development. The use of NSS carries a risk of leaving microscopic tumor residuals behind and may contribute to a poorer control of local disease. Yet other risk factors, in addition to a higher local stage, must be involved as well, because DFS remained worse for bilateral cases even when only local stage I and II tumors were compared with stage I and II unilateral tumors.[1]

Underlying congenital malformations/syndromes were identified in 18% of our patients and may be responsible for a higher risk of developing metachronous tumors (5 of the 16 patients concerned experienced a tumor relapse). Some tumors might respond poorly to chemotherapy due to the presence of anaplasia.[4,12,16] A recent article on BWT patients registered in the NWTS-4 study reported that 14.4% had diffuse anaplasia, which is a significantly higher proportion than among cases of unilateral WT.[14] Our proportion of anaplastic tumors (12%) is consistent with the above authors' experience,[14] but these accounted only for 2 treatment failures observed. It is worth noting that the French group reporting the lowest incidence of anaplasia among BWT cases (4%) also obtained better outcomes, with an OS of 89%.[15]

Focusing on unfavorable histology, we confirmed that finding the blastemal-type WT at surgery after initial chemotherapy confers a worse prognosis as well (6 of 8 patients relapsed), supporting the intensification of adjuvant therapy for this histological subtype adopted in the current SIOP 2001 study.

Given the value of preoperative chemotherapy in all BWTs (although some cases in our own and other series were managed with primary resection),[9-11,14] the most effective drug combination remains to be established. According to the literature, the most frequently used preoperative chemotherapy consisted of 2-drug (VA) or 3-drug (VAD) regimens,[4] depending partly on objective factors (any presence of distant metastases or tumor thrombi), but more often on the responsible physician's subjective criteria,[12-14,17] as seen in our experience too. In the report from our French colleagues, doxorubicin was added if response after the initial VA regimen was unsatisfactory when patients were assessed in terms of the feasibility of NSS.[15] A recent article on 188 synchronous BWTs reported that 61 of 129 patients initially treated with 2 drugs were switched to a different regimen (usually VAD) due to an unsatisfactory response.[14]

We observed a trend toward a better DFS in nonmetastatic BWT patients treated with VAD as preoperative chemotherapy (83% ± 8%) versus patients treated with VA (65% ± 7%), but this was not statistically significant. It is worth mentioning that our study, like others, was retrospective in nature and the decision to add other drugs to a VA backbone might have been biased by the common practice of adding drugs for less responsive or initially more advanced cases. However, because most patients initially treated with VAD had local stage III tumors (10 of 28, as opposed to 9 of 42 treated with VA alone), we can cautiously infer that adding doxorubicin is likely to be of some benefit. Our data seem to suggest that administering 3 instead of 2 drugs did not significantly reduce the number of total nephrectomies, although patients given doxorubicin as well might represent a selected population with more extensive bilateral renal involvement.

Another important issue in BWT is how long preoperative therapy should be, and its duration has varied considerably between different reports (eg, 114 days in the NWTS-4 study, 80 days in the French SIOP study). Prolonging preoperative therapy without a documented tumor response raises several concerns, as the report by Shamberger et al pointed out,[17] among them the risk of anaplastic transformation. Failure to respond to chemotherapy generally stems from 2 histological conditions, ie, anaplasia or mature stromal differentiation,[17-19] and both demand an attempt at complete resection (or at least at obtaining tissue to define tumor types), although they carry a different prognosis. A review by the German

Pediatric Oncology and Hematology Group reported that maximal tumor shrinkage was achieved within the first 12 weeks of chemotherapy, and continuing pre-resection chemotherapy any longer is unlikely to further facilitate conservative resections.[19] In our experience, prolonging preoperative chemotherapy beyond 3 months did not increase the proportion of definitive bilateral NSS (18 of 43 [42%] children underwent bilateral NSS after preoperative chemotherapy lasting less than 3 months as opposed to 19 of 37 [51%] children treated for more than 3 months).

We found that the attitude to the use of radiotherapy varied considerably, often differing from the generally accepted principles on radiotherapy for unilateral tumors. It is noteworthy that 12 of 28 patients classified as having stage III tumors received no local radiotherapy (5 of 12 patients eventually relapsed locally), possibly because their physicians were concerned about late renal impairment. We cannot exclude that this violation may partially account for the unsatisfactory DFS registered in our stage III cases. This decision to spare stage III patients local radiotherapy has been reported in other experiences as well.[15] A more standardized use of radiotherapy is an open issue that needs to be addressed in a comprehensive, prospective clinical trial.

The generally shared current surgical approach is to preserve more renal tissue by adopting a more conservative approach wherever possible. BWT may arise as an isolated abnormality within relatively normal kidneys, or as a tumor within a diffusely abnormal renal parenchyma highly prone to developing further tumors. The prevalence of nephrogenic rests is much higher in BWT, diffuse hyperplastic perilobar nephrogenic rests being particularly associated with synchronous BWT.[20] With time, however, even diffusely abnormal kidneys (as seen in Beckwith-Wiedemann syndrome, for instance) seem to lose their malignant potential, thus justifying a conservative surgical approach rather than ablative surgery, removing only frankly malignant tissue, when systemic chemotherapy is used.[21]

The overall rate of complete nephrectomies in our sample (50% of patients) was no lower than in other experiences,[11,14] but it coincided with an unjustifiably high rate of local recurrences (involving 20% of our patients; 8.2% in the NWTS-4 study,[22] and 10% in the recent French report[15]). This may reflect the fact that cases were managed at many different hospitals, ie, whereas 2 institutions treated nearly half the patients, the others were managed by another 16 institutions over a period of 2 decades. Consistent with this picture, in our series there was also a far from negligible rate of medical and surgical fatal complications (5 cases), that probably betrays a lack of experience. This finding may be a valid argument for treating children with BWT at selected referral centers. It is worth noting, on the other hand, that the highest rate of bilateral conservative procedures was reported in an experience from a single, expert institution.[23]

Breslow et al recently reported that the long-term risk of renal failure in BWT approached 15% at 15 years of follow-up. One weakness of our analysis lies in the lack of a full set of data on the patients' long-term renal function.[5]

Conclusions

The shortage of formal studies by cooperative groups, such as our AIEOP experience, may contribute to the heterogeneity of the treatments administered for BWT and the unsatisfactory level of evidence for treatment decision-making purposes. Some subjectivity for adding doxorubicin to a VA chemotherapy backbone in our sample means that caution is needed when it comes to commenting on the influence of using the 2 or 3 drugs on surgical (ie, the rate of bilateral NSS) or global outcome; a prospective evaluation of different preoperative chemotherapy regimens remains the right way forward. We suggest that blastemal-type histology is a significant reason why the outcome for BWT is worse than that for unilateral tumor.

Given the very low incidence of BWT in children, a formal international clinical trial will be needed to answer all the questions remaining in this field.

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