Pediatric Blood & Cancer

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RESEARCH ARTICLE

Anti-Tumor Activity of Paclitaxel-Containing Regimens in Recurrent/Refractory Wilms Tumor

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Received: 21 April 2025 | **Revised:** 17 June 2025 | **Accepted:** 1 July 2025

Keywords: nephroblastoma | paclitaxel | recurrent | relapse | taxane | Wilms tumor

ABSTRACT

Background: The Pediatric Oncology Group P9262 Phase 2 study of single-agent paclitaxel demonstrated one complete response (CR), one partial response (PR), and four with stable disease (SD) among 15 patients with recurrent Wilms tumor (WT). Based on this activity, paclitaxel-containing regimens have been used as salvage therapy for treatment-refractory WT. We conducted a multi-institutional retrospective study to further characterize the clinical activity of paclitaxel-containing regimens in recurrent WT.

Methods: Twelve institutions submitted anonymized data from patients with relapsed WT treated with paclitaxel. Response after one or two cycles of a paclitaxel-containing regimen was reported according to Response Evaluation Criteria in Solid Tumors.

Results: Twenty-eight patients with a median age at diagnosis of 5.5 years (range: 3 months to 31.9 years) were reported. Twenty had non-anaplastic WT; eight had diffuse anaplasia (DA). Stage at diagnosis was I ($n = 1$), II ($n = 1$), III ($n = 11$), IV ($n = 14$), and V ($n = 1$). Patients received a mean of 8.5 anticancer drugs (range: 6–12) before paclitaxel, including eight who received high-dose therapy/stem cell transplant. Paclitaxel ($n = 13$) or nab-paclitaxel ($n = 15$) were predominantly administered in combination with other agents, most commonly doxorubicin and/or gemcitabine. Eleven of 26 patients with measurable disease had a partial response (7 = non-anaplastic; 4 = DA), four had stable disease, and 11 had progressive disease. Two patients without measurable

Abbreviations: COG, Children's Oncology Group; CR, complete response; DA, diffuse anaplasia; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; REDCap, Research Electronic Data Capture; SD, stable disease; SIOP, International Society of Paediatric Oncology; WT, Wilms tumor.

This paper was previously presented at the International Society of Paediatric Oncology (SIOP) meeting in Honolulu, HI, October 2024 (Groisser et al. *Pediatric Blood & Cancer*, 2024; 71:e31444, S321); https://doi.org/10.1002/pbc.31444.

disease maintained a complete response for 12 and 16 months. The mean duration without progression was 7.6 months (range: 1–35 months).

Conclusions: Paclitaxel-containing regimens appear to be active against heavily pretreated WT with either non-anaplastic or DA histology. Prospective studies are warranted to formally evaluate the efficacy of paclitaxel-based therapies.

1 | Introduction

The treatment of Wilms tumor (WT) has been a major success in pediatric oncology, with a 5-year overall survival (OS) rate of approximately 92% using multimodal therapy [1]. However, there are patient subgroups for whom OS is less than 50%, including those with newly diagnosed Stage IV WT with diffuse anaplasia (DA), first relapse of WT after receiving three or more agents as primary therapy, and multiply recurrent WT [2]. More effective therapeutic options should be explored for such patients with recurrent or refractory disease.

The current approach to recurrent WT relies on agents to which patients were not previously exposed. Regimens containing cyclophosphamide, ifosfamide, carboplatin, doxorubicin, and etoposide have significantly improved outcomes after first recurrence, with 5-year OS of 50%–70%, depending on how many agents were included in initial treatment [3–7]. Topotecan and irinotecan have also demonstrated activity against WT [8–11] and are currently being evaluated in combination with other agents for first recurrence of WT in the Children's Oncology Group (COG) AREN1921 study [12]. Patients with a second or third recurrence have more limited treatment options, and outcomes are poor, with 1-year event-free survival (EFS) estimates ranging between 10% and 20% [8]. Meta-analyses have explored the utility of high-dose chemotherapy and autologous stem cell rescue in patients with recurrence, with inconclusive results [13, 14]; there is a clear need for new therapies.

Taxanes, a class of cytotoxic agents that stabilize microtubules and inhibit cell division, are active in a variety of solid tumors and are commonly used for adult patients with carcinomas and sarcomas. Several case reports of young adult patients with WT have demonstrated a response to paclitaxel-containing regimens [15–17]. Moreover, the Pediatric Oncology Group P9262 Phase 2 study of single-agent paclitaxel demonstrated one complete response (CR), one partial response (PR), and four with stable disease (SD) among 15 patients with recurrent WT, for a clinical benefit rate of 40% [18]. Based on this signal of antitumor activity, some pediatric oncologists have been using paclitaxel or nab-paclitaxel, an albumin-conjugated form of paclitaxel, for patients with multiply recurrent or treatment-refractory WT. We report the results of a retrospective study to document the clinical characteristics and outcomes of patients who had recurrent or refractory WT and received paclitaxel-containing regimens.

2 | Methods

Pediatric oncology centers known to have administered paclitaxel or nab-paclitaxel to patients with recurrent/refractory WT were identified and invited to participate. Institutional review board (IRB) approval or exempt status was obtained at each participating institution prior to data collection. Patients of any age with WT who had undergone treatment with paclitaxel-containing regimens up to March 2024 were eligible for inclusion. Clinical or research team members at each site accessed medical records to extract relevant data.

A centralized Research Electronic Data Capture (REDCap) database hosted at Children's National Hospital was used for collecting and managing patient data. This included demographic information, tumor characteristics, details of prior treatments, specifics of the paclitaxel-containing regimens, clinical responses according to Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, and outcomes. All data were anonymized before entry to ensure patient confidentiality. Descriptive analyses were conducted on response rates by tumor histology and paclitaxel regimen used. EFS was defined as the time from the start of paclitaxel therapy to tumor relapse, progression, or most recent follow-up. The time was calculated by adding the duration of paclitaxel therapy before the best response was achieved to the duration of the best response, which were the data points collected. Progression/Relapse within the first cycle of paclitaxel-based therapy was counted as progression at 3 weeks. OS was defined as the time from initiation of paclitaxel-based therapy to the time of death or most recent follow-up. Kaplan–Meier curves were generated using GraphPad Prism software.

3 | Results

Twenty-eight patients with recurrent WT were identified across 12 pediatric centers—11 in the United States and one in Israel. Demographic and clinical features at diagnosis are described in Table 1. Eighteen patients underwent immediate nephrectomy upon initial diagnosis, whereas 10 received pre-operative chemotherapy. Among the 18 who underwent immediate nephrectomy, histology was favorable in 12 and anaplastic in six. Among the 10 patients who received pre-operative chemotherapy, histology according to the International Society of Paediatric Oncology (SIOP) criteria [19, 20] was as follows: intermediate-risk ($n = 4$), diffuse anaplasia ($n = 2$), blastemal-type ($n = 1$), and non-anaplastic not otherwise specified ($n = 3$). Initial stage distribution at the time of diagnosis using the COG staging system was Stage I ($n = 1$; 3.6%), Stage II ($n = 1$; 3.6%), Stage III ($n = 11$; 39.3%), Stage IV ($n = 14$; 50%), and Stage V ($n = 1$; 3.6%).

Initial clinical characteristics and therapy given prior to administration of paclitaxel-containing therapy are summarized in Table 2. All patients were heavily pretreated. The duration of therapy prior to paclitaxel was not ascertained, and some patients lacked clear distinctions between one treatment and

TABLE 1 | Summary of demographic and clinical data.

Total number of patients	28
Median age at diagnosis (months)	66.5
Age range (months)	3–383
Sex	
Male	15 (53.6%)
Female	13 (46.4%)
Race	
White	26 (92.8%)
Black/African American	2 (7.1%)
Histology and timing of surgery	
Non-anaplastic	20 (71.4%)
Immediate nephrectomy with favorable histology	12
Pre-operative chemotherapy blastemal-type	1
Pre-operative chemotherapy for intermediate risk	4
Pre-operative chemotherapy not otherwise specified	3
Diffuse anaplasia	8 (28.6%)
Immediate nephrectomy	6
Pre-operative chemotherapy for diffuse anaplasia	2
Initial stage (COG staging system)	
I	1 (3.6%)
II	1 (3.6%)
III	11 (39.3%)
IV	14 (50%)
V	1 (3.6%)

the next. Patients received a mean of 8.5 different systemic chemotherapeutic agents before paclitaxel therapy. Eight patients received high-dose chemotherapy with autologous stem cell transplant (HDCT). All patients had also undergone radiation therapy (26 with treatment of initial disease and 18 at relapse, including the two who had not originally received radiation) and at least one surgical intervention prior to receiving paclitaxel. The best response before initiating paclitaxel was CR in 23 patients, partial response (PR) in one patient, and progressive disease (PD) throughout treatment in four patients.

Details of the paclitaxel-containing therapy, tumor response, and outcome are summarized in Table 3. The 28 patients received a variety of paclitaxel- (n = 13) or nab-paclitaxel (n = 15)-containing regimens. Nine patients were treated with nab-paclitaxel in combination with gemcitabine, eight received paclitaxel or nab-paclitaxel combined with doxorubicin, and five received a regimen that included nab-paclitaxel, gemcitabine, and doxorubicin. Two patients were treated with paclitaxel in combination with topotecan, and one patient each received paclitaxel combined with doxorubicin and carboplatin, paclitaxel combined with carboplatin and SAHA, or paclitaxel combined with carboplatin and gemcitabine. One patient received paclitaxel alone. Paclitaxel-containing therapy was administered on 21-day (n = 12) or 28-day (n = 16) cycles. Most patients received doses of 125 mg/m^2 on Days 1, 8, 15 (n = 15) or 240–250 mg/m^2 during Week 1 on variable days (n = 9); one patient each received doses of 40, 80, 100, or 175 mg/m^2. Patients received a mean of 3.5 cycles, with a median of three and a range of 1–10.

Of the 26 patients with measurable disease at initiation of paclitaxel-containing therapy, 11 patients (42.3%) demonstrated PR and four (15.3%) stable disease (SD) after one or two cycles. Eleven patients (42.3%) experienced PD. The best response achieved at any time after treatment with paclitaxel-containing regimens (including other agents) was recorded as four CR, seven PR, four SD, and 11 PD. It was not possible to measure the duration of response specifically to the paclitaxel-containing regimens, because most responders received other treatments after response to paclitaxel was documented. Two patients without measurable disease maintained CR for 12 and 16 months, the latter with ongoing CR at the time of data collection. The mean duration of time after starting paclitaxel-containing therapy without disease progression was 7.6 months.

Response rates to the different paclitaxel treatment regimens varied, as summarized in Table 4. Six of 13 patients (46.2%) had an objective response (PR) to paclitaxel regimens versus five of 13 (38.5%) to nab-paclitaxel regimens. Among nine patients treated with nab-paclitaxel and gemcitabine, two achieved a PR (22.2%) and seven experienced PD. Of eight patients who received (nab)paclitaxel and doxorubicin, five achieved a PR (62.5%) and three had PD. Of three patients treated with the combination of nab-paclitaxel, gemcitabine, and doxorubicin, two had PR (66.7%) and one had SD. Responses were observed in both favorable (7/20; 35%) and anaplastic (4/8; 50%) histology WT, as summarized in Table 5. Among eight patients who previously received HDCT, three had PR, one had SD, three had PD, and one, without measurable disease at the time of paclitaxel initiation, had durable CR at 16 months post-paclitaxel therapy.

Patient 14, who had diffuse anaplastic WT, was initially treated with aggressive front-line therapy, followed by multiple relapse therapies including ifosfamide, carboplatin, and etoposide, and high-dose chemotherapy with stem cell rescue. This patient subsequently had near-complete or very good partial responses of relapsed, metastatic disease in lungs, liver, and abdomen/pelvis on three separate occasions to nab-paclitaxel over several years.

At the time of data collection, 22 patients were deceased, three were alive with disease, and three were alive without evidence of disease. At 12 months from initiation of paclitaxel therapy, the EFS estimate was 15.6% (95% confidence interval [CI]: 4.9%–31.5%) and the OS estimate was 44.5% (95% CI: 25.4%–61.9%) (Figure 1).

4 | Discussion

Our retrospective study highlights the potential efficacy of paclitaxel-containing chemotherapy regimens in the treatment of recurrent WT in a heavily pretreated patient population. Among 26 patients who had measurable disease at the start of

TABLE 2 | Clinical and treatment data prior to paclitaxel therapy.[a]

Patient number	Histology	Initial stage	Sites of metastasis	Chemotherapy received prior to paclitaxel (# agents)	High-dose therapy/SCT prior to paclitaxel	Best response to therapy prior to paclitaxel
1	Non-anaplastic NOS	IV	Lung, IVC thrombus	DD-4A; VI; ICE; RIST; Cy/Top (11)	No	CR
2	Non-anaplastic NOS	IV	Lung	DD-4A; ICE + topotecan; VIT (9)	No	CR
3	Non-anaplastic NOS	IV	Lung	DD-4A; ICE + VI; cabozantinib; VITB (10)	Yes	CR
4	Diffuse anaplasia (received pre-operative chemotherapy)	V	Lung, liver, regional LN, distant LN	UH-2; VIT (7)	No	PR
5	Diffuse anaplasia	IV	Lung, regional LN, abdomen	DD-4A; UH-1; ICE + VI; ponatinib; topotecan (10)	No	CR
6	Favorable	III	Lung, pleural + extrapleural to left hemithorax, contralateral kidney	DD-4A; ICE + topotecan; VI; Cy/Top (10)	No	CR
7	High-risk blastemal	III	Lung	DD-4A; ICE + VI; Cy/Top + TAA-specific T cells (10)	Yes	CR
8	Diffuse anaplasia	IV	Lung, regional LN	UH-1; VIT + Cy/Top; vincristine/dactinomycin (9)	No	CR
9	Favorable	III	Lung	DD-4A; ICE; VI; Cy/Top; lenvatinib/everolimus (11)	No	CR
10	Diffuse anaplasia (received pre-operative chemotherapy)	IV	Lung, liver, regional LN, distant LN, bone	DD-4A; ICE + VI; Cy/Top; cabozatinib (10)	Yes	CR
11	Favorable	III	Abdomen (multiple intra-abdominal masses), liver	DD-4A; CCE; VI; ICE (8)	No	PR
12	Favorable	IV	Lung	Regimen M; ICE+ VI; Cy/Top (8)	Yes	CR
13	Favorable	IV	Lung, regional LN	Regimen M; carboplatin/ etoposide, irinotecan (7)	No	CR
14	Diffuse anaplasia	IV	Liver, lung, regional LN	UH-3; IT, palbociclib; ICE; pembrolizumab/decitabine/axitinib (12)	Yes	CR
15	Favorable	III	Lung, abdomen	DD-4A; ICE + Cy/Top; IT (10)	No	CR
16	Favorable	IV	Lung, regional LN	Regimen M; ICE + VI; IT/nab-rapamycin; IT/sirolimus (10)	Yes	CR
17	Favorable	III	Lung, mediastinal LN	DD-4A; ICE; Cy/Top; CCE; sorafenib; VI (10)	No	CR
18	Diffuse anaplasia	IV	Lung, regional LN	UH-3 (6)	No	PD
19	Favorable	III	Lung, pelvis	DD-4A; UH-3; VIT (8)	No	PD
20	Diffuse anaplasia	IV	Lung, abdomen	DD-4A; VDC; ICE;VI (8)	No	PD
21	Favorable	I	Lung	EE-4A; VDC + IE; carboplatin/topotecan; VIT (10)	No	CR

(Continues)

TABLE 2 | (Continued)

Patient number	Histology	Initial stage	Sites of metastasis	Chemotherapy received prior to paclitaxel (# agents)	High-dose therapy/SCT prior to paclitaxel	Best response to therapy prior to paclitaxel
22	Intermediate risk	III	Lung, contralateral kidney	EE-4A; Regimen I (6)	No	CR
23	Intermediate risk	III	Abdomen	VAD; DD-4A; CCE + VI (7)	No	CR
24	Intermediate risk	IV	Lung, regional LN	Regimen M; carboplatin/irinotecan (7)	Yes	CR
25	Favorable	II	Lung, abdomen	EE-4A; Regimen I; carboplatin/irinotecan, topotecan (9)	No	PD
26	Intermediate risk	III	Lung	DD-4A; CCE; VI (7)	No	CR
27	Favorable	IV	Lung, regional LN, liver	Regimen M; carboplatin + VI (7)	Yes	CR
28	Diffuse anaplasia	III	Abdomen, paraspinal, lung, liver, bone	DD-4A; ICE + Cy/Top; VITB (11)	No	CR

Abbreviations: CCE, cyclophosphamide/carboplatin/etoposide; Cy/Top, cyclophosphamide/topotecan; DD-4A, vincristine/dactinomycin/doxorubicin; EE-4A, vincristine/dactinomycin; ICE, ifosfamide/carboplatin/etoposide; IT, irinotecan/temozolomide; IVC, inferior vena cava; LN, lymph node; NOS, not otherwise specified; Regimen I, vincristine/doxorubicin/cyclophosphamide/etoposide; Regimen M, vincristine/dactinomycin/doxorubicin/cyclophosphamide/etoposide; RIST, rapamycin/irinotecan/dasatinib/temozolomide; TAA, tumor-associated antigen; UH-1, vincristine/doxorubicin/cyclophosphamide/carboplatin/etoposide; UH-3, vincristine/doxorubicin/cyclophosphamide/carboplatin/etoposide/irinotecan; VI(T)(B), vincristine/irinotecan/temozolomide/bevacizumab.

[a]All patients received surgery and radiation therapy prior to paclitaxel administration.

paclitaxel-based chemotherapy, 42.3% had an objective response, and two patients treated adjuvantly without measurable disease were without progression for 12 and 16 months. The EFS and OS estimates at 1 year were 15.6% (95% CI: 4.9%–31.5%) and 44.5% (95% CI: 25.4%–61.9%), respectively. This is similar to a heavily pretreated WT population included in a Phase 2 study of topotecan, in which EFS and OS estimates at 1 year were 16.4% ± 6.1% and 29.5% ± 8.3%, respectively [8].

The response rate to paclitaxel-containing regimens is noteworthy because no new classes of chemotherapeutic agents with efficacy in treating WT have been identified since the camptothecins, topotecan and irinotecan, were first studied almost 20 years ago [8, 9, 11]. A systematic review of 257 patients with recurrent WT who enrolled in 79 Phase 1 and 2 studies showed objective responses in 22 patients (8.5%), including 15/62 (24%) who received camptothecin-containing regimens [21]. The identification of paclitaxel combinations as potentially effective for WT is therefore consequential, offering a new option in a landscape where therapeutic advancements have been sparse.

The contribution of paclitaxel to the reported responses cannot be directly measured. The Pediatric Oncology Group P9262 Phase 2 study of paclitaxel showed an objective response rate of 13% with a clinical benefit rate of 40% when those with SD were included [18]. Studies with other taxanes have had variable results in WT, with the caveat that in the context of Phase 1 evaluations, the dosages or administration schedules may not have been optimal. Nab-Paclitaxel was not found to be active in four relapsed WTs, although a high-grade renal tumor not otherwise specified exhibited a partial response [22]. Docetaxel was not found to have activity in WT preclinically or clinically, with no responses in nine patients with recurrent WT [21, 23]. Although no response to docetaxel was evident in limited preclinical xenograft testing, a complete response was seen to cabazitaxel in the WT xenograft assessed, suggesting that response may vary depending on the particular taxane [23]. To our knowledge, cabazitaxel has only been tested on one patient with relapsed WT with no response [24]. Ixabepilone is an epothilone B analog that functions analogously to taxanes via tubulin binding and microtubule stabilization. There were no objective responses among 12 WT patients treated on Phase 1/2 studies of ixabepilone conducted by the COG, although one patient who had been treated with six prior regimens remained on treatment for 38 cycles with stable disease [25, 26].

In breast cancer, paclitaxel and doxorubicin are used in combination because the agents have different mechanisms of action and toxicity profiles [27–29]. Preclinical studies have suggested additive or synergistic effects of doxorubicin and paclitaxel in breast cancer cell lines and indicate that the sequence of delivery is important [30]. Our data suggest that paclitaxel combinations containing doxorubicin produced higher response rates (5/8 responses = 62.5%) than other regimens, although comparisons are limited by the small sample size and heterogeneity of tumor characteristics and prior treatments received. Decades-old response data for doxorubicin in recurrent WT collectively showed a response rate of 50%–60% [31–35], but those patients mostly received only vincristine and dactinomycin before doxorubicin. All patients in our series

TABLE 3 | Patient-level paclitaxel response data grouped by treatment regimen.

Patient number	Histology	Disease status at start of paclitaxel-containing regimen	Paclitaxel-containing regimen received (simplified)	Dose of paclitaxel (mg/m^2/dose)	Response to paclitaxel-containing therapy (cycle after which response recorded)	Best response after paclitaxel-containing therapy (includes other therapies)	Number of cycles of paclitaxel-containing therapy	Duration of best response (months)	Time from initiation of paclitaxel to follow-up (months)	Vital status
21	Favorable	PD	Paclitaxel	100	SD	SD	6	6	21	Deceased
1	Non-anaplastic NOS	PD	Paclitaxel/Doxorubicin	250	PR (2)	PR	3	4	10	Deceased
7	High-risk blastemal	PR	Paclitaxel/Doxorubicin	250	PR (2)	CR	6	3	18	Deceased
9	Favorable	PD	Paclitaxel/Doxorubicin	250	PR (2)	PR	4	2	11	Deceased
12	Favorable	PD	Paclitaxel/Doxorubicin	250	PR (2)	CR	6	35 (ongoing)	35	Alive, no evidence of disease
2	Non-anaplastic NOS	PD	Paclitaxel/Doxorubicin	250	PD	PD	1	N/A	12	Deceased
4	Diffuse anaplasia (received pre-operative chemotherapy)	PR	Paclitaxel/Doxorubicin	250	PD	PD	1	N/A	1	Deceased
11	Favorable	PD	Paclitaxel/Doxorubicin	250	PD	PD	1	N/A	1	Deceased
5	Diffuse anaplasia	PR	Nab-Paclitaxel/Doxorubicin	125	PR (2)	PR	3	2	6	Deceased
14	Diffuse anaplasia	PD	Nab-Paclitaxel/Gemcitabine	125	PR (1)	CR	4	6	16	Alive with disease
28	Diffuse anaplasia	PD	Nab-Paclitaxel/Gemcitabine	125	PR (2)	PR	3	2 (ongoing)	3	Alive with disease
10	Diffuse anaplasia (received pre-operative chemotherapy)	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	1	N/A	1	Deceased
18	Diffuse anaplasia	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	1	N/A	3	Deceased

(Continues)

TABLE 3 | (Continued)

Patient number	Histology	Disease status at start of paclitaxel-containing regimen	Paclitaxel-containing regimen received (simplified)	Dose of paclitaxel (mg/m^2/dose)	Response to paclitaxel-containing therapy (cycle after which response recorded)	Best response after paclitaxel-containing therapy (includes other therapies)	Number of cycles of paclitaxel-containing therapy	Duration of best response (months)	Time from initiation of paclitaxel to follow-up (months)	Vital status
19	Favorable	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	3	N/A	3	Deceased
20	Diffuse anaplasia	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	1	N/A	3	Deceased
24	Intermediate risk	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	2	N/A	7	Deceased
25	Favorable	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	2	N/A	4	Deceased
27	Favorable	PD	Nab-Paclitaxel/Gemcitabine	125	PD	PD	1	N/A	2	Deceased
15	Favorable	PD	Nab-Paclitaxel/ Doxorubicin/Gemcitabine	125	PR (1)	PR	3	1	5	Deceased
26	Intermediate risk	PD	Nab-Paclitaxel/ Doxorubicin/Gemcitabine	125	PR (2)	CR	10	12	69	Deceased
3	Non-anaplastic NOS	PD	Nab-Paclitaxel/ Doxorubicin/Gemcitabine	125	SD	SD	9	9	14	Deceased
6	Favorable	CR	Nab-Paclitaxel/ Doxorubicin/Gemcitabine	125	CR	CR	3	16 (ongoing)	16	Alive, no evidence of disease
16	Favorable	CR	Nab-Paclitaxel/ Doxorubicin/Gemcitabine	125	CR	CR	6	12	24	Alive, no evidence of disease
23	Intermediate risk	PD	Paclitaxel/Topotecan	240	PR (2)	PR	2	2	10	Alive with disease
22	Intermediate risk	PD	Paclitaxel/Topotecan	240	SD	SD	2	2	16	Deceased
8	Diffuse anaplasia	PR	Paclitaxel/Doxorubicin/ Carboplatin	40	PR (2)	PR	7	2	23	Deceased
17	Favorable	PD	Paclitaxel/Gemcitabine/ Carboplatin	80	PD	PD	1	N/A	2	Deceased
13	Favorable	PD	Paclitaxel/Carboplatin/ Vorinostat	175	SD	SD	8	14	25	Deceased

Abbreviation: NOS, not otherwise specified.

TABLE 4 | Response by paclitaxel regimen.

Paclitaxel-containing regimen	Number of patients	Responses to 1–2 cycles	Response rate
Nab-Paclitaxel/Gemcitabine	9	2 PR, 7 PD	22.2%
(Nab)-Paclitaxel/Doxorubicin	8	5 PR, 3 PD	62.5%
Nab-Paclitaxel/Gemcitabine/Doxorubicin	5	2 PR, 1 SD plus 2 durable CR (no measurable disease at start of paclitaxel therapy)	40%
Paclitaxel/Topotecan	2	1 PR, 1 SD	50%
Paclitaxel/Doxorubicin/Carboplatin	1	1 PR	100%
Paclitaxel/Carboplatin/SAHA	1	1 SD	0%
Paclitaxel/Carboplatin/Gemcitabine	1	1 PD	0%
Paclitaxel	1	1 SD	0%
Paclitaxel ± others	13	6 PR, 3 SD, 4 PD	46%
Nab-Paclitaxel + others	15	5 PR, 1 SD, 7 PD2 durable CR (no measurable disease at start of paclitaxel therapy)	39%

TABLE 5 | Response by histology.

Histology	Number of patients	Response to 1–2 cycles	Response rate
Non-anaplastic	20	7 PR, 4 SD, 7 PD2 durable CR (no measurable disease at start of paclitaxel therapy)	39%
Anaplastic	8	4 PR, 4 PD	50%

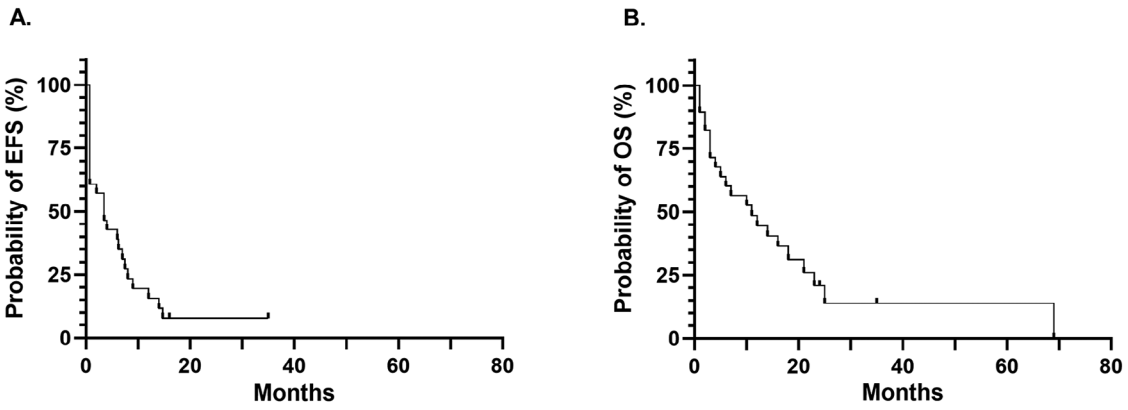

FIGURE 1 | Event-free survival (EFS) (A) and overall survival (OS) (B) curves from the time of initiation of paclitaxel-containing therapy.

previously received doxorubicin in addition to multiple other agents. We are skeptical that doxorubicin alone would produce the response rate we observed in such a heavily pretreated population.

There is precedent for studying drug combinations in high-risk or recurrent WT without knowing the single-agent activity of the drugs. Examples are the vincristine/irinotecan combination that was recently found to induce a response in 79% of patients with newly diagnosed Stage IV anaplastic Wilms tumor [9], and the cyclophosphamide/topotecan combination that demonstrated responses in two of six patients with recurrent WT across the Phase 1 and 2 studies conducted by the Pediatric Oncology Group [36, 37]. Both vincristine/irinotecan and cyclophosphamide/topotecan are being studied further in the COG AREN1921 study of treatment of children with newly diagnosed anaplastic histology and recurrent favorable histology WT [12].

The strength of this study is the relatively large case series of a rare patient population, which provides a more robust dataset of paclitaxel treatment in patients with refractory/recurrent WT than previous reports. Additionally, the focus on a population of heavily pretreated patients with recurrent WT offers valuable insights into the potential utility of paclitaxel in a challenging clinical setting where treatment options are limited. Limitations

of the study include the retrospective design and the potential for selection bias, given that only institutions where patients were known to have been treated with paclitaxel were invited to participate. Additionally, the variability in the paclitaxel regimens used, including differences in combination partners and dosing schedules, complicates the interpretation of the results. These factors limit the ability to draw definitive conclusions about the efficacy of paclitaxel without further study.

In summary, this multi-institutional case series suggests that paclitaxel-containing chemotherapy regimens including doxorubicin and/or gemcitabine are active in patients with recurrent, heavily pretreated favorable histology and anaplastic WT. Prospective studies are warranted to formally evaluate the efficacy of paclitaxel-based therapies and identify the subgroups of patients who may benefit.

Acknowledgments

The authors thank Alex's Army Childhood Cancer Foundation and the Rakan Stormer Wilms Tumor Research Fund for their invaluable support of this research. The authors also thank the clinical research coordinators who assisted with data extraction. Michael V. Ortiz is an employee of Memorial Sloan Kettering Cancer Center/MSK Kids and is supported by the NIH/NCI Cancer Center Support Grant P30-CA008748.

Conflicts of Interest

All authors declare no conflicts of interest.

References

1. "NCCR*Explorer: An Interactive Website for NCCR Cancer Statistics," National Cancer Institute, September 26, 2024, https://nccrexplorer.ccdi.cancer.gov.

2. M. V. Ortiz, C. Koenig, A. E. Armstrong, et al., "Advances in the Clinical Management of High-risk Wilms Tumors," *Pediatric Blood & Cancer* 70, no. S2 (2023): e30342, https://doi.org/10.1002/pbc.30342.

3. F. Spreafico, K. P. Jones, M. H. Malogolowkin, et al., "Treatment of Relapsed Wilms Tumors: Lessons Learned," *Expert Review of Anticancer Therapy* 9, no. 12 (2009): 1807–1815, https://doi.org/10.1586/ERA.09.159.

4. D. M. Green, C. A. Cotton, M. Malogolowkin, et al., "Treatment of Wilms Tumor Relapsing After Initial Treatment With Vincristine and Actinomycin D: A Report From the National Wilms Tumor Study Group," *Pediatric Blood & Cancer* 48, no. 5 (2007): 493–499, https://doi.org/10.1002/pbc.20822.

5. M. Malogolowkin, C. A. Cotton, D. M. Green, 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," *Pediatric Blood & Cancer* 50, no. 2 (2008): 236–241, https://doi.org/10.1002/pbc.21267.

6. E. A. Mullen, Y. Y. Chi, E. Hibbitts, et al., "Impact of Surveillance Imaging Modality on Survival After Recurrence in Patients With Favorable-histology Wilms Tumor: A Report From the Children's Oncology Group," *Journal of Clinical Oncology* 36, no. 34 (2018): 3396–3403, https://doi.org/10.1200/JCO.18.00076.

7. N. Schneller, N. Daw, W. Throckmorton, et al., "Outcomes of Relapsed Favorable-histology Wilms Tumor in Non-clinical Trial Setting," *Pediatric Blood & Cancer* 72, no. 1 (2025): e31347, https://doi.org/10.1002/pbc.31347.

8. M. L. Metzger, C. F. Stewart, B. B. Freeman, et al., "Topotecan Is Active Against Wilms' tumor: Results of a Multi-institutional Phase II Study," *Journal of Clinical Oncology* 25, no. 21 (2007): 3130–3136, https://doi.org/10.1200/JCO.2007.10.9298.

9. N. C. Daw, Y. Y. Chi, J. A. Kalapurakal, et al., "Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study," *Journal of Clinical Oncology* 38, no. 14 (2020): 1558–1568, https://doi.org/10.1200/JCO.19.01265.

10. J. A. Hol, M. M. van den Heuvel-Eibrink, N. Graf, et al., "Irinotecan for Relapsed Wilms Tumor in Pediatric Patients: SIOP Experience and Review of the Literature—A Report From the SIOP Renal Tumor Study Group," *Pediatric Blood & Cancer* 65, no. 2 (2018): e26849, https://doi.org/10.1002/pbc.26849.

11. R. Venkatramani, M. H. Malogolowkin, and L. Mascarenhas, "Treatment of Multiply Relapsed Wilms Tumor With Vincristine, Irinotecan, Temozolomide and Bevacizumab," *Pediatric Blood & Cancer* 61, no. 4 (2014): 756–759, https://doi.org/10.1002/pbc.24785.

12. J. I. Geller, A. L. Hong, K. L. Vallance, et al., "Children's Oncology Group's 2023 Blueprint for Research: Renal Tumors," *Pediatric Blood & Cancer* 70 (2023): e30586, https://doi.org/10.1002/pbc.30586.

13. T. C. Ha, F. Spreafico, N. Graf, et al., "An International Strategy to Determine the Role of High Dose Therapy in Recurrent Wilms' Tumour," *European Journal of Cancer* 49, no. 1 (2013): 194–210, https://doi.org/10.1016/j.ejca.2012.07.010.

14. A. Presson, T. B. Moore, and P. Kempert, "Efficacy of High-Dose Chemotherapy and Autologous Stem Cell Transplant for Recurrent Wilms' Tumor: A Meta-Analysis," *Journal of Pediatric Hematology/Oncology* 32 (2010): 454–461.

15. A. Italiano, N. Sirvent, J. F. Michiels, F. Peyrade, J. Otto, and A. Thyss, "Tumour Response to paclitaxel in an Adult With Relapsed Nephroblastoma," *Lancet Oncology* 6, no. 4 (2005): 252–253, https://doi.org/10.1016/S1470-2045(05)70098-X.

16. R. K. Ramanathan, J. T. Rubin, N. P. Ohori, and C. P. Belani, "Dramatic Response of Adult Wilms Tumor to Paclitaxel and Cisplatin," *Medical and Pediatric Oncology* 34, no. 4 (2000): 296–298, https://doi.org/10.1002/(SICI)1096-911X(200004)34:4⟨296::AID-MPO20⟩3.0.CO;2-P.

17. S. Ozaki, N. Takigawa, E. Ichihara, et al., "Favorable Response of Heavily Treated Wilms' tumor to Paclitaxel and Carboplatin," *Onkologie* 35, no. 5 (2012): 283–286, https://doi.org/10.1159/000338532.

18. M. Harris, C. Hurwitz, J. Sullivan, E. Larsen, and C. Pratt, "Taxol in Pediatric Solid Tumors: A Pediatric Oncology Group (POG) Phase II Study (POG#9262)," POG, 1999.

19. J. S. Dome, E. J. Perlman, and N. Graf, "Risk Stratification for Wilms Tumor: Current Approach and Future Directions," *American Society of Clinical Oncology Educational Book* 2014 (2014): 215–223, doi:10.14694/EdBook_AM.2014.34.215.

20. G. M. Vujanić, B. Sandstedt, D. Harms, et al., "Revised International Society of Paediatric Oncology (SIOP) Working Classification of Renal Tumors of Childhood," *Medical and Pediatric Oncology* 38, no. 2 (2002): 79–82, https://doi.org/10.1002/mpo.1276.

21. J. Brok, K. Pritchard-Jones, J. I. Geller, and F. Spreafico, "Review of Phase I and II Trials for Wilms' Tumour—Can We Optimise the Search for Novel Agents?," *European Journal of Cancer* 79 (2017): 205–213, https://doi.org/10.1016/j.ejca.2017.04.005.

22. L. Moreno, M. Casanova, J. C. Chisholm, et al., "Phase I Results of a Phase I/II Study of Weekly Nab-Paclitaxel in Paediatric Patients With Recurrent/Refractory Solid Tumours: A Collaboration With Innovative Therapies for Children With Cancer," *European Journal of Cancer* 100 (2018): 27–34, https://doi.org/10.1016/j.ejca.2018.05.002.

23. C. P. Reynolds, M. H. Kang, J. M. Maris, et al., "Initial Testing (stage 1) of the Anti-Microtubule Agents Cabazitaxel and Docetaxel, by the Pediatric Preclinical Testing Program," *Pediatric Blood & Cancer* 62, no. 11 (2015): 1897–1905, https://doi.org/10.1002/pbc.25611.

24. P. E. Manley, T. Trippett, A. A. Smith, et al., "A Phase 1/2 Dose-finding, Safety, and Activity Study of cabazitaxel in Pediatric Patients With Refractory Solid Tumors Including Tumors of the Central Nervous System," *Pediatric Blood & Cancer* 65, no. 9 (2018): e27217, https://doi.org/10.1002/pbc.27217.

25. B. C. Widemann, W. Goodspeed, A. Goodwin, T. Fojo, F. M. Balis, and E. Fox, "Phase I Trial and Pharmacokinetic Study of Ixabepilone Administered Daily for 5 Days in Children and Adolescents With Refractory Solid Tumors," *Journal of Clinical Oncology* 27, no. 4 (2009): 550–556, https://doi.org/10.1200/JCO.2008.17.6644.

26. S. Jacobs, E. Fox, M. Krailo, et al., "Phase II Trial of Ixabepilone Administered Daily for Five Days in Children and Young Adults With Refractory Solid Tumors: A Report From the Children's Oncology Group," *Clinical Cancer Research* 16, no. 2 (2010): 750–754, https://doi.org/10.1158/1078-0432.CCR-09-1906.

27. L. Gianni, L. Viganò, A. Locatelli, et al., "Human Pharmacokinetic Characterization and in Vitro Study of the Interaction Between Doxorubicin and Paclitaxel in Patients With Breast Cancer," *Journal of Clinical Oncology* 15, no. 5 (1997): 1906–1915, https://doi.org/10.1200/JCO.1997.15.5.1906.

28. P. Dombernowsky, J. Gehl, M. Boesgaard, T. P. Jensen, and B. V. Jensen, "Paclitaxel and Doxorubicin, a Highly Active Combination in the Treatment of Metastatic Breast Cancer," *Seminars in Oncology* 23, no. 1 (1996): 13–18.

29. E. Baltali, M. K. Altundağ, N. Güler, et al., "Paclitaxel and Doxorubicin Combination in the First-Line Treatment of Metastatic Breast Cancer," *Tumori* 88, no. 3 (2002): 200–203, https://doi.org/10.1177/030089160208800304.

30. D. Amadori, G. L. Frassineti, W. Zoli, et al., "Doxorubicin and Paclitaxel (Sequential Combination) in the Treatment of Advanced Breast Cancer," *Oncology (Williston Park)* 11, no. 4 (1997): 30–33.

31. A. H. Ragab, W. W. Sutow, D. M. Komp, K. A. Starling, G. M. Lyon, and S. George, "Adriamycin in the Treatment of Childhood Solid Tumors. A Southwest Oncology Group Study," *Cancer* 36, no. 5 (1975): 1567–1571, https://doi.org/10.1002/1097-0142(197511)36:5⟨1567::AID-CNCR2820360505⟩3.0.CO;2-I.

32. F. Fossati Bellani, M. Gasparini, and G. Bonadonna, "Letter to the Editor Adriamycin in Wilms's Tumor Treated With Chemotherapy Previously," Vol 1, Pergamon Press, 1975.

33. C. Tan, E. Etcubanas, N. Wollner, et al., "Adriamycin—An Antitumor Antibiotic in the Treatment of Neoplastic Diseases," *Cancer* 32, no. 1 (1973): 9–17, https://doi.org/10.1002/1097-0142(197307)32:1⟨9::aid-cncr2820320102⟩3.0.co;2-6.

34. R. M. O'Bryan, J. K. Luce, R. W. Talley, J. A. Gottlieb, L. H. Baker, and G. Bonadonna, "Phase II Evaluation of Adriamycin in human Neoplasia," *Cancer* 32, no. 1 (1973): 1–8, https://doi.org/10.1002/1097-0142(197307)32:1⟨1::aid-cncr2820320101⟩3.0.co;2-x.

35. A. Cangir, S. K. Morgan, V. J. Land, J. Pullen, S. A. Starling, and R. Nitschke, "Combination Chemotherapy With Adramycin (NSC-123127) and Dimethyl Triazeno Imidazole Carboxamide (DTIC) (NSC-45388) in Children With Metastatic Solid Tumors," *Medical and Pediatric Oncology* 2, no. 2 (1976): 183–190, https://doi.org/10.1002/mpo.2950020208.

36. R. L. Saylors, C. F. Stewart, W. C. Zamboni, et al., "Phase I Study of Topotecan in Combination With Cyclophosphamide in Pediatric Patients With Malignant Solid Tumors: A Pediatric Oncology Group Study," *Journal of Clinical Oncology* 16, no. 3 (1998): 945–952, https://doi.org/10.1200/JCO.1998.16.3.945.

37. R. L. Saylors, K. C. Stine, J. Sullivan, et al., "Cyclophosphamide Plus Topotecan in Children With Recurrent or Refractory Solid Tumors: A Pediatric Oncology Group Phase II Study," *Journal of Clinical Oncology* 19, no. 15 (2001): 3463–3469, https://doi.org/10.1200/JCO.2001.19.15.3463.