Pediatr Blood Cancer 2008;50:236–241

Treatment of Wilms Tumor Relapsing After Initial Treatment With Vincristine, Actinomycin D, and Doxorubicin. A Report From the National Wilms Tumor Study Group

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Objective. We evaluated the use of alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide in children entered on National Wilms Tumor Study (NWTS)-5 who were diagnosed between August 1, 1995 and May 31, 2002 and who relapsed after chemotherapy with vincristine, actinomycin D, and doxorubicin (VAD) and radiation therapy (DD-4A). ***Patients And Methods.*** One hundred three patients who relapsed or had progressive disease after initial VAD chemotherapy and radiation therapy were registered on stratum C of the NWTS-5 Relapse protocol. Twelve patients were not evaluable: five due to insufficient data, six due to major protocol violations, and one for refusal of therapy. Among the 91 remaining patients, 14 with stage V Wilms tumor (WT), 1 with contralateral relapse, and 16 who did not achieve a complete response (CR) to the initial three-drug chemotherapy were not included in this analysis. Relapse treatment included alternating courses of the drug pairs cyclophosphamide/etoposide and carboplatin/etoposide, surgery, and radiation therapy. ***Results.*** The outcomes of 60 patients were analyzed. The lung was the only site of relapse for 33 patients; other sites of relapse included the operative bed, the abdomen, and liver. Four-year event-free survival (EFS) and overall survival (OS) were 42.3 and 48.0% respectively for all patients and were 48.9 and 52.8% for those who relapsed in the lungs only. Thrombocytopenia was the most frequent toxicity. ***Conclusion.*** These results demonstrate that approximately one-half of children with unilateral WT who relapse after initial treatment with VAD and radiation therapy can be successfully retreated. Pediatr Blood Cancer 2008;50:236–241. © 2007 Wiley-Liss, Inc.

Key words: chemotherapy; phase II clinical trials; radiation oncology; solid tumors; Wilms tumor (WT)

INTRODUCTION

The outlook for children with Wilms tumors (WT) has improved dramatically with the advent of multi-modal therapy, and survival rates currently are approaching 90% [1–3]. Although the overall relapse rate for children with WT has decreased to less than 15%, the long-term survival for patients with recurrent disease remains less than 30% [4,5]. Factors associated with a favorable outcome after relapse include low stage (I/II) at diagnosis, treatment with vincristine and actinomycin D only, no prior radiotherapy, favorable histology, relapse to lung only, and interval from nephrectomy to relapse $\geq$12 months. All other patients have a poor outcome and a high risk of treatment failure [4,6]. Recently, loss of heterozygosity (LOH) for chromosomal markers for 16q was shown to be an important additional prognostic factor in children with favorable or anaplastic histology WT [7].

This article contains Supplementary Material available at http://www.interscience.wiley.com/jpages/1545-5009/suppmat.

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Grant sponsor: USPHS; Grant number: CA-42326.

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Received 29 November 2006; Accepted 16 April 2007

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DOI 10.1002/pbc.21267

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The poor outcome of patients with recurrent WT after initial treatment with vincristine, actinomycin D, doxorubicin (VAD), and radiation therapy led to the investigation of the activity of ifosfamide, etoposide, and platinum analogs as single agents or in combination for the treatment of such patients [8–18]. These studies demonstrated response rates greater than 40%. However, the responses were not durable and the outcome continued to be poor.

This study was designed to further evaluate the effect of various clinical and biological variables on the outcome of children with relapsed WT; and to determine if the use of alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide improved the event-free survival (EFS) of children with WT who relapsed after chemotherapy with VAD and radiation therapy (DD-4A).

PATIENTS AND METHODS

National Wilms Tumor Study (NWTS)-5 (NWTS-5) was a multi-institutional clinical trial for patients less than 16 years of age at diagnosis with specific renal neoplasms that were diagnosed between August 1, 1995 and May 31, 2002. All patients underwent an initial nephrectomy after completing a pre-operative assessment. The histology of the tumors was classified as previously described [19]. A stage was assigned employing the National Wilms Tumor Study Group (NWTSG) surgical–pathological staging system [20], which was modified prior to the start of NWTS-5.

Children who received regimen DD-4A (stages I–IV favorable histology WT and stage II or III focal anaplastic WT) as initial treatment [21] and had relapse or progression of their tumor could be registered on the NWTSG protocol ''Treatment of Relapsed Patients'' (POG 9444; CCG 4942) in stratum C. This protocol received Institutional Review Board (IRB) approval at 135 institutions, 32 institutions did not have IRB approval, frequently because IRB approval was not sought, and 85 institutions had unknown IRB approval status.

All patients underwent radiographic evaluation of the chest, abdomen, and pelvis. Histological confirmation of relapse was strongly suggested, but was not a protocol entry requirement. Institutional operative notes and NWTSG retrieval surgical forms for initial and subsequent relapse surgery procedures were reviewed to confirm the site of relapse and surgical findings that related to the assigned relapse stage.

The NWTSG pathologist reviewed microscopic slides, institutional pathology reports, and NWTSG retrieval pathology forms. A relapse stage was assigned as outlined in Supplemental Table I. Adverse prognostic factors (APF) were evaluated following the guidelines utilized by the French Society of Pediatric Oncology [22] (Supplemental Table II).

All patients received induction therapy (Supplemental Figure 1). Those who showed at least minimal response to therapy went on to have surgical resection of the tumor followed by radiation therapy of all sites of disease. Radiation therapy was initiated within 9 days from surgery during consolidation phase following previously published guidelines [23]. Patients who had no evidence of disease (CR–complete response) after surgery and/or radiation therapy received consolidation (Supplemental Figure 2) and maintenance therapy (Supplemental Figure 3). G-CSF 5 μg/kg/day was given subcutaneously beginning 24 hr after the last dose of chemotherapy and given until ANC $\geq$10,000 and past the nadir for myelosuppression or a minimum of 1 week.

The quantitative measure of therapeutic outcome used for this study was the percentage of patients who were alive and disease free 4 years following their registration on the retrieval protocol. Analyses were performed using actuarial methods to estimate the EFS and overall survival (OS) curves. The data were analyzed using standard statistical methods, including product limit estimates of survival curves and the log rank test [24,25]. Standard errors were computed using Greenwood's formula [26]. These methods all account for the fact that not all patients had complete follow-up.

RESULTS

One hundred three patients who relapsed or had progressive disease after initial chemotherapy with VAD and radiation therapy (DD-4A) were registered on stratum C of the NWTSG protocol ''Treatment of Relapsed Patients'' (POG 9444; CCG 4942) between August 1, 1995 and May 31, 2002. Twelve patients were not evaluable: five due to insufficient data, six due to major protocol violations, and one for refusal of therapy. Among the 91 remaining patients, 14 with stage V WT, 1 with contralateral relapse, and 16 who did not achieve a CR to the initial three-drug chemotherapy, were not included in this analysis. Seven of the 16 had persistent disease while receiving regimen DD-4A (e.g., histologically recognizable WT in delayed nephrectomy specimen) and nine had progression of disease while receiving regimen DD-4A. Two had initial stage III disease and 14 had stage IV disease. Three (one stage III and two stage IV) underwent initial nephrectomy, one (stage IV) underwent partial nephrectomy, and the remaining 12 underwent initial biopsy only. Twelve of the patients had received radiation therapy prior to initiation of stratum C treatment. During this same time period, additional 35 patients who were registered on POG 9440/CCG 4941 (NWTS-5—Therapeutic Trial & Biology Study) and were treated using regimen DD-4A developed recurrent disease, but were not registered on POG 9444/CCG 4942. Of these, five had bilateral WT at diagnosis, three developed a contralateral relapse, and three had persistent disease, leaving a comparison group of 24 patients, of whom 17 had stage III and 7 had stage IV WT.

Thirty-two of the 60 patients included in this analysis were females. Fifty-six patients had favorable histology WT, three focal anaplasia, and one diffuse anaplasia. One patient had initial stage II WT, 39 had stage III WT, and 20 had stage IV WT. Thirty-six patients (60%) relapsed within 12 months from initial nephrectomy. The lung was the only site of relapse in 33 patients; other sites of relapse included the operative bed, the abdomen, and liver. Additional characteristics of the patients are shown in Supplemental Table III. One operative bed relapse and one combined operative bed and lung relapse occurred among the four patients who did not receive post-nephrectomy renal fossa irradiation.

The 4-year EFS and OS were 42.3 and 48.0% respectively for all patients and were 48.9 and 52.8% for those who relapsed in the their lungs only (Figs. 1 and 2). The 4-year EFS for those with relapse to lung only was not significantly different from the 4-year EFS for all other relapse patients ($P = 0.28$). Table I shows the 4-year EFS and OS according to site(s) of relapse, gender, age at diagnosis, initial tumor stage, time from nephrectomy to relapse, relapse stage, and number of APF. Females had a better 4-year EFS and OS (54.7 and 58.7%) than males (28.6 and 38.0%). Patients with 0–3 APF at study entry had better 4-year EFS than those with $\geq$4 APF. Most patients had a relapse stage of IV and thus relapse stage provided little additional prognostic information.

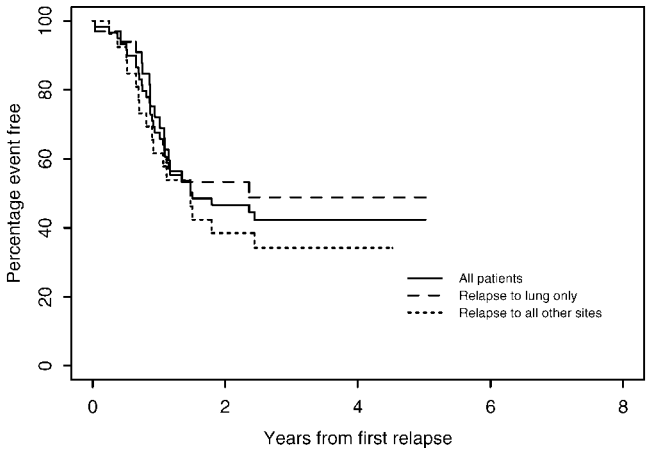

Fig. 1. Stratum C event-free survival (EFS): Solid line—all patients (N = 60) (4-year EFS—42.3; 95% confidence interval (CI)—29.3, 54.8); dashed line—relapse to lung only (N = 33) (4-year EFS—48.9; 95% CI—30.3, 65.1); dotted line—relapse to all other sites (N = 27) (4-year EFS—34.2; 95% CI—17.0, 52.3) (*P*-value (log rank) = 0.24).

Information regarding LOH for markers of chromosome 1p and 16q was available for 40 of the 60 patients included in this analysis. Of these patients, three had LOH at both 1p and 16q, four had LOH at only 1p, six had LOH at only 16q, and 27 were without LOH at both 1p and 16q (Table I). LOH did not adversely affect 4-year event free or OS, but the number of patients included in this analysis was small. One of the patients with LOH for markers of 1p and 16q had a second relapse and died.

The reported toxicity of treatment for relapsed disease is detailed in Table II. The most frequent toxicity was profound thrombocytopenia that led to discontinuation of maintenance therapy for 15 patients (37% of those who received maintenance therapy). One patient developed myelodysplastic syndrome and one patient died after the first course of maintenance therapy as the result of influenza B virus and Aspergillus infection. Significant nephrotoxicity was not observed. The protocol required administration of six 12-week courses of maintenance chemotherapy. The actual number of courses received by the 41 patients who received maintenance chemotherapy was: ≤one—12 patients; >one and ≤two—14 patients; >two and ≤three—three patients; four—three patients; five—two patients; six—seven patients. Parental refusal was the reason for treatment discontinuation for three patients after one course and two patients after two courses. Fifteen patients had treatment discontinued due to prolonged hematological toxicity (two courses—eight patients; three courses—three patients; four courses—two patients; five courses—two patients).

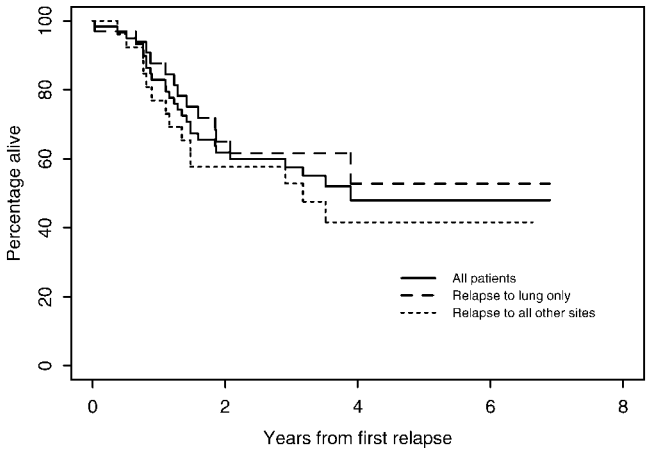

Fig. 2. Stratum C overall survival (OS): Solid line—all patients (N = 60) (4-year OS—48.0; 95% confidence interval (CI)—32.6, 61.8); dashed line—relapse to lung only (N = 33) (4-year OS—52.8; 95% CI—29.7, 71.5); dotted line—relapse to all other sites (N = 27) (4-year OS—41.6; 95% CI—21.3, 60.9) (*P*-value (log rank) = 0.328).

The overall 4-year survival of the 24 patients who were registered on POG 9440/CCG 4941 (NWTS-5—Therapeutic Trial & Biology Study) and who were initially treated with regimen DD-4A and relapsed and were, therefore, eligible for but were not registered on POG 9444/CCG 4942 (NWTS-5—Treatment of Relapsed Patients) was 60.9% (95% confidence interval (CI)—38.3%, 77.4%), compared to 46.9% (95% CI—33.7%, 59.1%) for all 76 patients registered on stratum C of POG 9444/CCG 4942 (Fig. 3).

Five of seven relapsed stage III patients who underwent autologous bone marrow transplantation (ABMT) survived as did five of ten treated with stratum C or similar chemotherapy. None of three relapsed stage IV patients who underwent ABMT survived and one of two survived who were treated with stratum C or similar chemotherapy.

One stage IV patient who developed a brain metastasis was treated with radiation therapy only and one stage IV patient who developed a pulmonary metastasis was treated with resection of the metastasis only.

The 4-year survival rate for the 16 registered patients who had disease persistence or progression was 43.8% (95% CI—19.8%, 65.6%) (Fig. 3). All seven with disease persistence survived and all nine with disease progression died.

DISCUSSION

WT is the most frequent malignant renal tumor in children, and the prognosis for children with this malignancy has improved dramatically in the past four decades. The relapse rate for children with WT has decreased significantly. The long-term survival for patients with relapsed disease was reported to be 24–30% [4,5], although one series reported survival of 74% of patients treated between 1984 and 2000 [27]. Prognostic factors associated with a worse outcome have been identified [4,6,27], facilitating administration of tailored therapy according to risk for recurrence after relapse therapy.

In an effort to improve survival rates, multiple agents and more intensive therapeutic regimens have been used in non-randomized trials to treat children with relapsed WT [8–17]. Although these studies have demonstrated response rates ranging from 42 to 73%, the responses were usually of short duration and the outcome has continued to be poor with EFS of 40–60% [18,27–29].

High-dose chemotherapy followed by autologous stem cell rescue has been used for the treatment of a small number of patients with high-risk relapsed WT. In one large study, five of eight patients with stage III or IV favorable histology WT were disease-free survivors 39+–82+ months after treatment for their first relapse with autologous stem cell transplantation. Two of the five disease-free survivors did not achieve a CR prior to autologous

TABLE I. Event-Free Survival (EFS) and Overall Survival (OS)

Site	Number of patients	Number of second events	4-year EFS (%)	Number of deaths	4-year survival (%)
All	60	33	42.3 (29.3, 54.8)	27	48.0 (32.6, 61.8)
Operative bed ± lung ± other	7	6	14.3 (0.7, 46.5)[a]	4	38.1 (6.1, 71.6)[b]
Liver ± other	6	5	16.7 (0.8, 51.7)[a]	4	33.3 (4.6, 67.6)[b]
Abdomen or pelvis ± lung	6	5	—	5	—
Lung only	33	16	48.9 (30.3, 65.1)[a]	13	52.8 (29.7, 71.5)
Lung and other	6	1	80.0 (20.4, 96.9)[a]	1	80.0 (20.4, 96.9)[b]
Other	2	0	—	0	—
Gender					
Male	28	20	28.6 (13.5, 45.6)[a]	17	38.0 (20.2, 55.7)[b]
Female	32	13	54.7 (34.7, 70.9)	10	58.7 (34.8, 76.4)
Age at diagnosis					
0–23 months	4	3	25.0 (0.9, 66.5)[a]	3	25.0 (0.9, 66.5)[b]
24–47 months	21	11	47.6 (25.7, 66.7)[a]	11	39.3 (13.9, 64.2)[b]
48+ months	35	19	41.0 (23.9, 57.4)	13	54.5 (33.3, 71.5)
Initial tumor stage					
II	1	0	—	0	—
III	39	18	51.8 (34.6, 66.6)	15	54.4 (34.2, 70.9)
IV	20	15	21.1 (6.6, 41.0)[a]	12	35.1 (14.6, 56.6)
Time from nephrectomy to relapse (months)					
0–6	9	5	44.4 (13.6, 71.9)[a]	4	53.3 (17.7, 79.6)[b]
7–12	27	18	28.5 (12.7, 46.6)[a]	17	29.6 (12.6, 48.8)[b]
>12	24	10	57.7 (35.5, 74.6)	6	65.8 (36.1, 84.2)
Relapse stage					
I	2	2	0[a]	2	0[b]
II	1	0	—	0	—
III	7	6	—	4	28.6 (1.4, 69.1)[b]
IV	50	25	47.6 (32.8, 60.9)	21	53.1 (36.4, 67.3)
Adverse prognostic factors					
0–1	25	10	56.9 (34.3, 74.3)[a]	7	65.1 (37.6, 82.8)
2–3	22	12	45.0 (23.9, 64.1)[a]	10	48.2 (22.9, 69.7)
>4	13	11	8.3 (0.5, 31.1)[a]	10	16.7 (2.6, 41.3)[b]
Loss of heterozygosity (LOH) 1p					
Yes	7	3	57.1 (17.2, 83.7)[a]	2	68.6 (21.3, 91.2)[b]
No	33	18	41.6 (24.2, 58.2)	15	48.9 (29.3, 66.0)
Loss of heterozygosity (LOH) 16q					
Yes	9	4	55.6 (20.4, 80.5)[a]	3	66.7 (28.2, 87.8)[b]
No	31	17	40.4 (22.3, 57.7)	14	47.6 (27.2, 65.5)
Loss of Heterozygosity (LOH) 1p and/or 16q					
LOH at 1p and 16q	3	1	—	1	—
LOH at 1p only	4	2	50.0 (5.8, 84.5)[a]	1	66.7 (5.4, 94.5)[b]
LOH at 16q only	6	3	50.0 (11.1, 80.4)[a]	2	66.7 (19.5, 90.4)[b]
No LOH at 1p or 16q	27	15	39.5 (20.5, 58.0)	13	44.8 (23.6, 64.0)

[a]Fewer than five patients event-free past 4 years; [b]fewer than five patients alive past 4 years.

TABLE II. Toxicities

Toxicity	Grade	Number of patients (%)
WBC count	3	8 (13%)
	4	23 (38%)
ANC	3	6 (10%)
	4	23 (38%)
Platelets	3	5 (8%)
	4	25 (42%)
Hemoglobin	3	19 (32%)
	4	13 (22%)
Infection	3	18 (30%)
	4	1 (2%)

stem cell transplantation [22]. A second study reported that five of nine patients with stage III or IV favorable histology WT were relapse-free survivors 31+–144+ months after treatment for their first relapse with autologous stem cell transplantation. Two of the five relapse-free survivors did not achieve a CR prior to autologous stem cell transplantation [30]. These studies suggest that high-dose chemotherapy followed by autologous stem cell rescue may be beneficial for some patients with recurrent WT, although a randomized trial comparing high-dose chemotherapy with ABMT to conventional post-relapse chemotherapy has not yet been conducted.

The best approach for the treatment of high-risk relapsed WT patients still needs to be defined. The present study was designed to

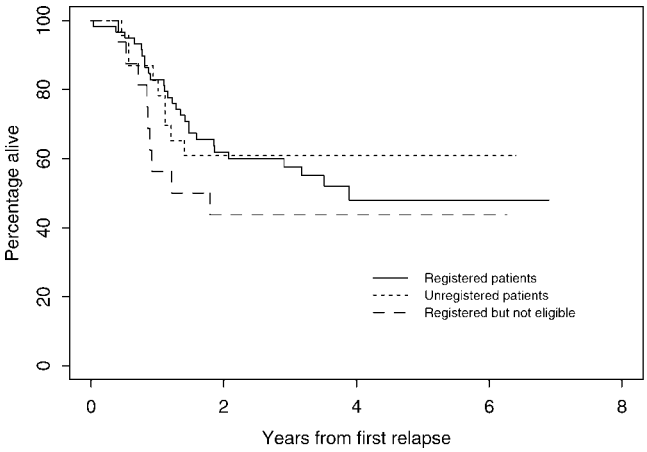

Fig. 3. Stratum C overall survival (OS): Solid line—registered patients (not progressive or persistent disease) (N = 60) (4-year OS—48.0; 95% confidence interval (CI)—32.6, 61.8); dashed line—registered patients who were not eligible for analysis (progressive or persistent disease) (N = 16) (4-year OS—43.8; 95% CI—19.8, 65.6); dotted line—all unregistered patients (not progressive or persistent disease) (N = 24) (4-year OS—60.9; 95% CI—38.3, 77.4) (*P*-value (log rank) = 0.414).

further evaluate the effect of various clinical and biological variables on the outcome of children with relapsed WT; and to determine if the use of alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide could improve the EFS of children with WT who relapsed after chemotherapy with VAD and radiation therapy (DD-4A). These results demonstrate that approximately one-half of children with unilateral WT who relapse after initial treatment with VAD and radiation therapy can be successfully rescued. Examination of the characteristics and outcome of eligible patients who were not registered on study demonstrated that patients with more APF were not preferentially entered on the study. The toxicity of the chemotherapy regimen was manageable. The development of a prospective international cooperative trial for the treatment of high-risk relapsed WT patients is necessary to determine if treatment with conventional intensive chemotherapy or with high-dose chemotherapy followed by autologous stem cell transplantation will be associated with a better outcome.

ACKNOWLEDGMENT

The authors thank the investigators of the Pediatric Oncology Group and the Children's Cancer Group and the many pathologists, surgeons, pediatricians, radiation oncologists, and other health professionals who managed the children entered on the National Wilms Tumor Studies.

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