Tolerability of ifosfamide-containing regimen in patients with high-risk renal and INI-1-deficient tumors

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Abstract

Background: Outcomes for children with high-risk renal (HRR) and INI-1-deficient (INI-) tumors are unacceptably poor. Concerns about excessive toxicity – as many are infants and/or undergo nephrectomy – have resulted in decreased chemotherapy dosing and omission of the nephrotoxic drug ifosfamide in collaborative group studies. As cause of death for children with these cancers remains overwhelmingly more from progressive disease rather than treatment toxicity, we examined the tolerability of an intensive ifosfamide-containing-regimen. **Procedure:** Retrospective review of children with HRR/INI- tumors treated at a single institution with vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide, carboplatin, etoposide (VDC-ICE) from 2006-2016. The primary outcome was regimen tolerability including kidney injury and grade 3-5 non-hematologic toxicities. **Results:** Fourteen patients with a median age of 1.7 years (range 0.1-10.5) treated with VDC-ICE were identified. Diagnosis included malignant rhabdoid tumor (n=9) [primary renal (n=2)]; diffuse anaplastic Wilms tumor (n=3); clear cell sarcoma of the kidney (n=1); and anaplastic chordoma (n=1). All children with primary renal tumors (43%) underwent complete (n=5) or partial nephrectomy (n=1) before chemotherapy. Nine (64%) completed all intended cycles of chemotherapy; n=5 (36%) did not due to disease progression. Unplanned hospitalizations occurred in 13 (93%) patients, most commonly for febrile neutropenia. No patient experienced severe organ toxicity, diminished renal function, treatment discontinuation due to toxicities, or treatment-related death. **Conclusions:** In children with HRR/INI- tumors, VDC-ICE chemotherapy was well-tolerated without excessive toxicities, even amongst young patients with solitary kidneys. Concerns about toxicity should not preclude an intensive ifosfamide-containing regimen from use in future trials in this population.

INTRODUCTION

Outcomes for children with advanced stage high-risk renal (HRR) tumors, such as malignant rhabdoid tumors (MRT), diffuse anaplastic Wilms tumors (DAWT), and clear cell sarcoma of the kidney (CCSK), are markedly worse than for favorable histology Wilms Tumor.[1-5] Large collaborative group trials, such as Children's Oncology Group's (COG) AREN0321, have improved outcomes for some children with HRR tumors using increasingly intensive, multi-agent chemotherapy regimens. Yet for MRT and other INI-1 deficient (INI-) tumors, which can also occur outside the kidney, outcomes remain dismal. Chemotherapy for HRR/INI- tumors typically combines common agents, such as vincristine, doxorubicin, cyclophosphamide, carboplatin, and etoposide. Prospective studies, including the National Wilms Tumor Study Group studies and COG AREN0321, have omitted ifosfamide from upfront use due to concerns about nephrotoxicity in these patients, many of whom require nephrectomy. Toxicity concerns have also limited therapy intensification strategies that have been successful in other aggressive pediatric malignancies.

Despite prospective trial avoidance of upfront ifosfamide, a few case studies have reported patients with MRT successfully treated using alternating cycles of vincristine, doxorubicin, and cyclophosphamide (VDC) and ifosfamide, carboplatin, and etoposide (ICE). However, ICE-containing therapies can be nephrotoxic and potentially difficult to tolerate in very young children, particularly those who receive a nephrectomy. These tolerability concerns have limited the use of ICE and other ifosfamide-containing regimens in patients with HRR/INI- tumors, despite its use for relapsed renal tumors and other aggressive pediatric solid tumors.[9-11] Further analysis is needed to evaluate the effectiveness and tolerability of VDC-ICE as front-line therapy in these children.

Beginning in 2006, our institution implemented a standard treatment plan, alternating cycles of VDC and ICE (hereafter referred to as VDC-ICE), for patients presenting with HRR/INI- tumors and offered it to patients who were not eligible for or refused an open clinical trial at the time of presentation. We now report upon the clinical course, complications, and toxicities experienced by our patients treated with this regimen.

METHODS

We retrospectively reviewed the medical records of pediatric patients treated at the Dana-Farber/Boston Children's (DF/BC) Cancer and Blood Disorders Center with the VDC-ICE treatment plan and diagnosed from January 2006 to December 2016. Patients were identified through a search of the Pediatric Patient Informatics Platform and electronic chemotherapy order entry reports detailing treatment plans. These reports were reviewed for their accuracy. Patients were excluded if – despite receiving a recommendation for this treatment plan or beginning this treatment plan at DF/BC – they completed the bulk of the treatment at another institution or had shared cared with another institution, as all details on toxicity were not available. General characteristics of these patients were captured as available but were not included in the analysis. Data collected on the population of interest included patient demographics, treatment plan, and clinical course, as well as complications, toxicities, and outcomes. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board.

VDC-ICE treatment plan

The core treatment plan was adapted from published dosing and administration schedules. The plan consists of eight alternating cycles of VDC and ICE given intravenously. Cycles of VDC consist of cyclophosphamide 1800-2100 (higher dose for MRT) mg/m^{2}given on day 1, doxorubicin 37.5 mg/m^2 given days 1 and 2 (or a single dose on day 1), and vincristine 1.5 mg/m^2 given days 1, 8, and 15 (or a single dose on day 1). Cycles of ICE consist of carboplatin at a target AUC of 6 mg/ml-min given on day 1, with ifosfamide 2000 mg/m^2 and etoposide 100 mg/m^2 given days 2, 3, and 4. Mesna was administered for bladder protection with all doses of cyclophosphamide or ifosfamide, per institutional standards. Growth factor with filgrastim or pegfilgrastim, and cardioprotection with dexrazoxane (dosed at 10 times the doxorubicin dose as 375 mg/m^2), were administered per institutional standards to all patients. Cycles were three weeks in duration, with an allowable interruption of up to two weeks for surgical resection of the primary or residual tumor. Radiation therapy was recommended concurrently with chemotherapy. Modifications in chemotherapy doses or changes to the order of chemotherapy cycles (e.g., giving consecutive ICE cycles to avoid anthracyclines concurrently with radiation) were at the discretion of the patient's oncologist. Supportive care often included aggressive and extended anti-emetic regimens and extended supplemental intravenous fluid replacement.

Tolerability, complications, and toxicity

The primary aim of this study was to describe the complications and toxicity associated with this treatment plan. Data were abstracted from the record, described categorically, and graded using the common terminology criteria for adverse events version 5 (CTCAE v5.0). Information abstracted included: unplanned hospitalizations and admissions to the intensive care unit (ICU), unplanned ambulatory clinic or emergency department (ED) visits (not for scheduled chemotherapy, routine examinations, or restaging); significant infections, such as central line-associated bloodstream infection, and treatment delays. A treatment delay was defined as an interval of greater than four weeks between chemotherapy cycles (one week longer than expected) or greater than five weeks if surgery was performed (two weeks longer than expected without

surgery). Organ toxicity (except for hematopoietic and transient minor elevation of liver function tests), admissions for fever and neutropenia, uncontrolled nausea, and vomiting were recorded and graded. Long-term toxicities (organ toxicities grades 3 and 4) and impact on growth were noted in follow-up until the last contact at the time of record abstraction.

Outcomes

Data examined included whether remission, relapse, or death from disease progression occurred and the patients' vital status at last contact.

Data collection and statistical analyses

Two trained pediatric oncology physicians (DJB and CIW) abstracted data from the patients' medical records using a standardized data collection form in REDCap, an electronic data management platform. The form was first pilot-tested by the two clinicians and modified to ensure the data of interest was collected. To ensure consistency, the two clinicians met before abstracting data and throughout data collection to reach consensus on definitions. Each clinician also independently reviewed two records that had been abstracted by the other and no discrepancies were found. Descriptive statistics were used to summarize patient demographics, clinical characteristics, toxicities, and outcomes, including frequencies and proportions for categorical variables and medians and ranges for continuous variables. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Fourteen patients received VDC-ICE therapy as described in Table 1. The median age at diagnosis was 1.7 years (range=0.1-10.5), and 50% were male (n=7) and 79% Caucasian (n=11). The most common diagnosis was non-kidney MRT (n=7), followed by DAWT (n=3), MRT of the kidney (n=2), CCSK (n=1), and anaplastic chordoma (n=1). Six patients had metastatic disease (stage IV), with the kidney (n=6) or soft tissue (n=6) being the most common primary disease sites. Five patients received previous treatment, and 6 patients underwent complete or partial nephrectomy prior to chemotherapy.

Therapy details

Chemotherapy and local control therapies are described in Table 2. Nine patients (64%) completed the intended 8 cycles of VDC-ICE chemotherapy. In the five remaining patients (36%), the planned treatment regimen was discontinued for disease progression. Three patients (21%) received additional chemotherapy concurrently with VDC-ICE. This additional chemotherapy for all three patients consisted of cycles of vincristine and irinotecan (VI) intermixed with VDC-ICE, as data emerged that the addition of VI improved outcome for patients with DAWT.

For the 9 patients who completed treatment, the median cumulative dose received was 6000 mg/m^2 of cyclophosphamide (range=4800-8400), 24 g/m^2 of ifosfamide (range=21-24), and 270 mg/m^2 of doxorubicin (range=135-450). All patients received dexrazoxane as cardio-protection with doxorubicin, and all received growth factor after each chemotherapy cycle.

Local control therapy consisted of surgery and/or radiation. Nine (64%) patients received radiation to the primary site of disease, and 3 (21%) received additional radiation to metastatic sites. Most (n=7/9; 78%) patients received radiation therapy concurrent with chemotherapy. Ten patients underwent some form of surgical resection, which was performed upfront, prior to chemotherapy initiation, in 6 patients. Complete surgical resection was achieved in 70% (n=7/10) of all patients who underwent resection and in 78% (n=7/9) of patients who received radiation therapy.

Complications and toxicity

Cycle-specific toxicities are described in Table 3. A total of 87 cycles of VDC or ICE were received; 45 were VDC cycles, and 42 were ICE cycles. Seven (16%) VDC cycles were associated with chemotherapy delays

compared to 4 (10%) ICE cycles. The most common reason for chemotherapy delay was delayed count recovery. Febrile neutropenia was the most common complication observed, seen in 20 (44%) VDC cycles and 18 (43%) ICE cycles. Unplanned hospitalizations were seen in 22 (49%) of VDC cycles and 22 (52%) of ICE cycles, most commonly due to febrile neutropenia. Similarly, 28 (62%) VDC cycles and 36 (86%) of ICE cycles were associated with an unplanned visit to the ED or clinic, for reasons such as blood product transfusions, fever evaluation, and symptom management.

VDC cycles were also associated with 1 (2%) electrolyte disturbance and 1 (2%) hemorrhagic cystitis, both grade 1. No VDC cycles led to acute kidney injury or resulted in the need for home hydration.

ICE cycles were further complicated by 1 (2%) grade 1 acute kidney injury (with rapid recovery) and 2 (5%) minor electrolyte disturbance. Five (12%) led to the use of pre-emptively arranged home hydration for future subsequent cycles after experiencing significant delayed nausea and vomiting post carboplatin in an initial cycle. No ICE cycles were associated with hemorrhagic cystitis.

Overall, among 14 patients treated with VDC-ICE therapy, 13 (93%) had an unplanned admission to the hospital (Supplemental Table S1). All patients had unplanned ED/clinic visits (Supplemental Table S1). Thirteen patients (93%) experienced at least one episode of Grade 3 febrile neutropenia, and 8 (57%) patients experienced grade 3 anorexia/malnutrition (Table 4). Other Grade 3 criteria observed included: nausea/vomiting/dehydration (n=7); diarrhea (n=1); hypotension in the setting of hematemesis (n=1); peripheral neuropathy (n=1); and bacteremia (n=1). No non-hematologic grade 4 or 5 toxicities were observed. Other complications patients experienced included acute kidney injury (n=1) and hepatotoxicity (n=2) (Table 3 and 4). For the patients with hepatotoxicity, tumor burden likely was a contributory factor. Hepatotoxicity occurred only in patients with underlying diagnosis of MRT of the liver. Two (14%) patients required escalation of care to the ICU during therapy (Supplemental Table S1), both of which were found to have progressive disease shortly after ICU admission. Another patient was transferred from a different institution to the ICU due to complications that began prior to their first cycle of VDC-ICE chemotherapy, so this ICU admission was not attributed to the treatment plan.

There was no documented ototoxicity or clinically significant cardiotoxicity, defined as a decrease in ejection fraction of greater than 15 percent. Seven patients (50%) experienced chemotherapy administration delays. Six (43%) patients had delays during VDC cycles, and 4 (29%) experienced delays during ICE cycles (Table 3). Eight patients (57%) required chemotherapy dose modifications, with the most commonly modified drug being vincristine (n=5), followed by doxorubicin (n=3), carboplatin (n=3), ifosfamide (n=2), and etoposide (n=2) (Supplemental Table S1). No treatment-related mortality was observed.

Outcomes

Of the 14 patients who received VDC-ICE chemotherapy, 8 (57%) achieved clinical remission (Supplemental Table S2). Eight patients (57%) experienced relapse or progressive disease, of which 50% had disease at a new site different than the original sites of disease. At the time of data collection, 56% (n=5) of patients with MRT were alive (including both patients with MRT of the kidney), as well as all patients with DAWT (n=3), CCSK (n=1), and anaplastic chordoma (n=1).

DISCUSSION

Across an 11-year period at our institution, fourteen patients (5 with single kidney) were treated with an intensive ifosfamide-containing VDC-ICE treatment plan. This regimen was well tolerated, with no patient experiencing toxicities severe enough to prevent completion of planned therapy, and no significant renal toxicity occurred in any patient. Although only 9 out of 14 patients completed all 8 intended cycles of chemotherapy, early termination of VDC-ICE chemotherapy was only due to disease progression, not lack of tolerability. There were no toxic deaths or severe organ toxicities. While examining outcomes was not our primary objective, our results add to existing evidence of an association of improved outcomes with the use of intensified treatment.

The COG clinical trial, AREN0321, found that chemotherapy regimens (UH-1 and UH-2) containing nearly

all of the same agents as VDC-ICE, with the notable omission of ifosfamide, improved relapse-free survival for stages II-IV DAWT. The UH-1 and UH-2 regimens were accompanied by significant treatment-related CTCAE grade 4 toxicities and mortality – with four patients with DAWT (6%) dying of toxicities – prompting a reduction in regimen intensity and eventual early termination of the trial. As VDC-ICE is similar or even more intense than UH-1 (Supplemental Table S3), we examined the toxicities experienced by our patients receiving VDC-ICE. Importantly, we did not observe any non-hematologic grade 4 or 5 toxicities. As the most significant complications of AREN0321 were related to cardiac and pulmonary dysfunction, we hypothesize that the universal use of the cardioprotectant dexrazoxane in our study, which was allowed but not recommended on AREN0321, may have contributed to the lack of grade 4 and 5 toxicities. However, future studies are needed to confirm this hypothesis. Additional supportive care, including administration of prophylactic infectious measures may have helped decrease infectious complications, but these were not administered in a standardized way. Kidney function may have been protected by extended home hydration implementation.

The potential nephrotoxicity of ifosfamide-containing regimens like VDC-ICE is a major concern in patients with HRR tumors, especially those with single kidneys. In our cohort, kidney injury was rare, with just a single episode of temporary grade 1 acute kidney injury due to an episode of dehydration associated with carboplatin-induced delayed nausea and vomiting, which resolved in 24 hours. Six of our patients had primary renal tumors, all of whom underwent bilateral partial or unilateral nephrectomies prior to the majority of their chemotherapy. All six completed the intended 8 cycles of VDC-ICE, making the lack of severe toxicity or renal insufficiency noteworthy in light of the inclusion of the potentially nephrotoxic ifosfamide in VDC-ICE as compared to the AREN0321 regimens. Possible explanations include improvements in antiemetic management with more widespread use of aprepitant and the ability to provide home hydration via nasogastric tube or intravenous fluids. We acknowledge that our institution's catchment area has excellent home nursing resources, enabling us to offer these options to our patients.

Despite meticulous supportive care, the VDC-ICE regimen is not without toxicities. Not surprisingly, given the myelosuppression expected with the agents and doses administered, all but one patient (who only received 3 cycles of VDC-ICE due to disease progression) experienced at least one CTCAE grade 3 toxicity, each having at least one hospitalization for febrile neutropenia. Half of our patients had grade 3 nausea/vomiting/dehydration, and more than half had anorexia requiring nutritional support through a nasogastric tube. Other significant toxicities were rare and limited to one episode of uncomplicated bacteremia, hepatotoxicity in patients with tumors of their livers, and admissions to the ICU. While 14% (2/14) of patients requiring ICU admission seems substantial, none were thought to be related to VDC-ICE chemotherapy.

Although all patients treated with this regimen required significant supportive care (e.g., unplanned ED/clinic visits, transfusion, and nutritional support), it appears that overall, the complications and toxicities observed in our cohort were manageable. Even though treatment delays of greater than a week were observed in 50% of our patients, these were mostly due to delayed count recovery. Furthermore, this is not entirely unexpected given the intensity of this regimen and does not justify considering this regimen as intolerable. Other regimens, such as standard of care for Ewing sarcoma (interval compressed alternating cycles of VDC and ifosfamide/etoposide), are also plagued by the need for significant symptomatic and supportive care, treatment delays, and admissions for febrile neutropenia. Yet, this regimen has been used for years as the standard of care for this disease, lasts longer than VDC-ICE (28 versus 24 weeks) and has higher cumulative doses of doxorubicin (375 mg/m^2), cyclophosphamide (8400 mg/m^2), ifosfamide (63 g/m^2), and etoposide (3500 mg/m^2).

Our findings are limited by the small number of patients and their management at our single institution. It is possible that the lack of toxic deaths we have seen is due to chance alone. For example, given toxic deaths on AREN0321 were rare, if the toxic death rate of VDC-ICE were comparable to UH-1 and UH-2 regimens, we would have expected to see just 1 toxic death in our 14 patients. Even discounting toxic death rates, it is notable that our patients experienced no grade 4 toxicities. Because these tumors are rare, the challenge of low patient numbers is difficult to overcome even through multicenter trials. Nevertheless, we

represent a high-volume center, and this is the largest cohort of patients with HRR/INI- tumors described with this chemotherapy regimen. The other similarly-sized cohort of pediatric oncology patients treated with VDC-ICE comprised patients with Ewing sarcoma who were much older, lacked renal tumors, and thus would have been expected to tolerate the regimen better than our cohort.[9]

Additionally, because this represents a retrospective analysis, controlling for differences in patient characteristics, treatment regimen administration, or supportive care is difficult. Each patient's treatment plan was developed by our center's disease-specific expert in renal tumors and MRT, with some patients receiving customized dosing or the addition of other chemotherapy agents based on individual characteristics. Therefore, whether our experience is generalizable remains an important question.

Our findings suggest that VDC-ICE chemotherapy can be safely used for children with HRR and INI-deficient tumors, with comparable toxicity to other widely accepted pediatric oncology regimens. Most notably, use of ifosfamide was tolerated without nephrotoxicity in a population generally thought of as being at unacceptably high-risk of renal toxicity. Despite the known activity of ifosfamide in HRR/INI- tumors, the use of post-nephrectomy ifosfamide has been reserved for the relapsed setting. Yet for patients with these aggressive malignancies, for whom death is overwhelmingly due to progressive and relapsed disease rather than treatment toxicity, withholding effective agents is difficult to justify. With our findings of excellent tolerance of VDC-ICE combined with no meaningful chance of post-relapse survival for patients with these tumors, inclusion of ifosfamide in upfront treatment regimens is imperative. The use of this regimen has been adopted as our standard of care for these rare malignancies and should be considered as a reasonable option until future studies identify more promising treatments. Furthermore, we believe this regimen warrants further evaluation at a greater scale through a prospective, multicenter clinical trial.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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TABLE 1. Patient characteristics

	Total patients (n=14)
Age at diagnosis (years), median (range)	1.7 (0.1-10.5)

	Total patients (n=14)
Gender (male), *n* (%)	7 (50)
Race, *n* (%)	
White	11 (79)
Asian	1 (7)
Other	2 (14)
Ethnicity, *n* (%)	
Not Hispanic or Latino	14 (100)
Hispanic or Latino	0 (0)
Diagnosis, *n* (%)	
Malignant rhabdoid tumor, non-kidney	7 (50)
Diffuse anaplastic Wilms tumor	3 (21)
Malignant rhabdoid tumor of the kidney	2 (14)
Clear cell sarcoma of the kidney	1 (7)
Anaplastic chordoma	1 (7)
Stage, *n* (%)	
I	0 (0)
II	1 (7)
III	6 (43)
IV	6 (43)
V	1 (7)
Primary site, *n* (%)	
Kidney	6 (43)
Liver	2 (14)
Soft Tissue	6 (43)
Previous treatment, *n* (%)	
Yes	5 (36)
No	9 (64)
Nephrectomy prior to chemotherapy, *n* (%)	6 (43)
Complete	5 (36)
Partial	1(7)

TABLE 2. Therapy details

	Total patients (n=14)	Total patients (n=14)	
Number of VDC-ICE cycles completed/patient	Number of VDC-ICE cycles completed/patient		
<8 cycles	<8 cycles	5 (36)	5 (36)
8 cycles	8 cycles	9 (64)	9 (64)
Additional concurrent regimen administered	Additional concurrent regimen administered		
Yes	Yes	3 (21)	3 (21)
No	No	11 (79)	11 (79)
Planned chemotherapy dose per cycle, median (range)	Planned chemotherapy dose per cycle, median (range)		
cyclophosphamide (mg/m^2)	cyclophosphamide (mg/m^2)	1500 (1200-2100)	1500 (1200-2100)
doxorubicin (mg/m^2)	doxorubicin (mg/m^2)	45 (45-75)	45 (45-75)

	Total patients (n=14)	Total patients (n=14)	
ifosfamide (gm/m^2)	ifosfamide (gm/m^2)	6 (6-6)	6 (6-6)
vincristine (mg/m^2)	vincristine (mg/m^2)	4.5 (2-4.5)	4.5 (2-4.5)
carboplatin (AUC target, mg/ml-min)	carboplatin (AUC target, mg/ml-min)	6 (6-6)	6 (6-6)
etoposide (mg/m^2)	etoposide (mg/m^2)	300 (300-300)	300 (300-300)
Received dexrazoxane	Received dexrazoxane	14 (100)	14 (100)
Received growth factor after every cycle	Received growth factor after every cycle	14 (100)	14 (100)
Cumulative chemotherapy dose (for patients who completed treatment), median (range)	Cumulative chemotherapy dose (for patients who completed treatment), median (range)		
cyclophosphamide (mg/m^2)	cyclophosphamide (mg/m^2)	6000 (4800-8400)	6000 (4800-8400)
ifosfamide (g/m^2)	ifosfamide (g/m^2)	24 (21-24)	24 (21-24)
doxorubicin dose (mg/m^2)	doxorubicin dose (mg/m^2)	270 (135-450)	270 (135-450)
Received radiation	Received radiation	9 (64)	9 (64)
Primary site, *n* (%)	Primary site, *n* (%)	9 (64)	9 (64)
Flank	Flank	2 (22)	2 (22)
Other	Other	7 (78)	7 (78)
Metastatic site, *n* (%)	Metastatic site, *n* (%)	3 (21)	3 (21)
Lung	Lung	2 (67)	2 (67)
Bone	Bone	1 (33)	1 (33)
Timing of radiation, *n* (%)	Timing of radiation, *n* (%)		
Pre-chemotherapy	Pre-chemotherapy	1 (11)	1 (11)
During chemotherapy	During chemotherapy	7 (78)	7 (78)
Post-chemotherapy	Post-chemotherapy	1 (11)	1 (11)
Age at radiation (years), median (range)	Age at radiation (years), median (range)	3.4 (1.6-11.2)	3.4 (1.6-11.2)
Underwent surgical resection, *n* (%)	Underwent surgical resection, *n* (%)	10 (71)	10 (71)
Complete resection	Complete resection	7 (54)	7 (54)
Gross resection	Gross resection	2 (15)	2 (15)
Unknown	Unknown	1 (8)	1 (8)
Timing of surgical resection, *n* (%)	Timing of surgical resection, *n* (%)		
Upfront	Upfront	6 (60)	6 (60)
After neoadjuvant chemotherapy	After neoadjuvant chemotherapy	4 (40)	4 (40)
Age at surgery (years), median (range)	Age at surgery (years), median (range)	1.7 (0.3-9.3)	1.7 (0.3-9.3)
Biopsy only, *n* (%)	Biopsy only, *n* (%)	4 (31)	4 (31)

Abbreviations: VDC-ICE, vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide, carboplatin, and etoposide.

TABLE 3. Cycle specific toxicity

	Cycles (n=87)	Cycles (n=87)
	VDC	ICE
Number of cycles received, *n*	45	42
Number of delayed cycles, *n* (%)	7 (16)	4 (10)
Delay reason, *n* (%)		
Delayed count recovery	5 (71)	2 (50)
Surgical recovery	1 (14)	1 (25)
Other complication	1 (14)	0(0)
Infection	0 (0)	0 (0)
Unknown	0 (0)	1 (25)
Febrile neutropenia, *n* (%)	20 (44)	18 (43)
Acute kidney injury, *n* (%)	0 (0)	1 (2)
Minor electrolyte disturbance, *n* (%)	1 (2)	2 (5)
Hemorrhagic cystitis, *n* (%)	1 (2)	0 (0)
Home hydration, *n* (%)	0 (0)	5 (12)
Unplanned hospital admission, *n* (%)	22 (49)	22 (52)
Reason for admission, *n* (%)		
Febrile neutropenia	17 (77)	16 (73)
Nausea/Vomiting/Dehydration	4 (18)	5 (23)
Other	11 (50)	8 (36)
Unplanned ED/clinic visit, *n* (%)	28 (62)	36 (86)

Abbreviations: VDC, vincristine, doxorubicin, and cyclophosphamide; ICE, ifosfamide, carboplatin, and etoposide; ED, emergency department.

TABLE 4. Grade 3 non-hematologic toxicities based on the common terminology criteria for adverse events

	Total patients (n=14)
Febrile neutropenia, *n* (%)	13 (93)
Anorexia/malnutrition, *n* (%)	8 (57)
Nausea/vomiting/dehydration, *n* (%)	7 (50)
Hepatotoxicity, *n* (%)	2 (14)
Hypotension, *n* (%)	1 (7)
Bacteremia, *n* (%)	1 (7)
Diarrhea, *n* (%)	1 (7)
Peripheral neuropathy, *n* (%)	1 (7)