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Phase II trial of gemcitabine and nab-paclitaxel in patients with recurrent Ewing sarcoma: A report from the National Pediatric Cancer Foundation

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Background: The combination of gemcitabine and docetaxel is often used to treat patients with recurrent sarcoma. Nab-paclitaxel is a taxane modified to improve drug exposure and increase intratumoral accumulation and, in combination with gemcitabine, is standard therapy for pancreatic cancer. Applying the dosages and schedule used for pancreatic cancer, we performed a phase II trial to assess the response rate of gemcitabine and nab-paclitaxel in patients with relapsed Ewing sarcoma.

Procedure: Using a Simon's two-stage design to identify a response rate of ≥ 35%, patients received nab-paclitaxel 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 i.v. on days 1, 8, and 15 of four-week cycles. Immunohistochemical analysis of archival tissue was performed to identify possible biomarkers of response.

Results: Eleven patients from four institutions enrolled, with a median age of 22 years (range, 14–27). Patients were heavily pretreated (median 3 prior regimens, range, 1–7). Thirty-five cycles were administered (median 2, range, 1–8). Accrual was stopped after 11 patients, due to only one confirmed partial response. Two other patients had partial responses after two cycles, but withdrew because of adverse effects or progression before confirmation of continued response. The predominant toxicity was myelosuppression, and four (36%) patients were removed due to hematologic toxicity despite pegfilgrastim and dose reductions. Expression of secreted protein, acidic and rich in cysteine (SPARC) and CAV-1 in archival tumors was not predictive of clinical benefit in this small cohort of patients.

Conclusions: In patients with heavily pretreated Ewing sarcoma, the confirmed response rate of 9% was similar to multi-institutional studies of gemcitabine and docetaxel.

Keywords

AYA; chemotherapy; Ewing sarcoma; gemcitabine; nab-paclitaxel; pediatric; phase II clinical trials

1 | INTRODUCTION

Although the majority of adolescents and young adults with localized Ewing sarcoma can become long-term survivors, more effective therapies are needed for patients who present with metastatic disease or whose tumors recur after completing primary therapy.[1] Particularly attractive treatment options include chemotherapy combinations using commercially available drugs for which there is a biological rationale, preclinical evidence of synergy, and a previously established regimen for outpatient administration.

Over the past two decades, the combination of gemcitabine and docetaxel (GEM/DOC) has been used to treat both soft-tissue and bone sarcomas. The most common schedule is to administer gemcitabine on day 1 followed by both gemcitabine and docetaxel on day 8 of a three-week cycle. In an international phase III trial of adults with locally advanced or metastatic soft-tissue sarcoma, progression-free survival (PFS) with GEM/DOC was similar to doxorubicin,[2] which is standard front-line therapy for these patients. Modest activity has also been seen in bone sarcoma, with nearly all studies focusing on salvage therapy after

relapse. Five single-institution studies including a variety of tumor types have shown a collective objective response rate of 29% in the 16 cumulative patients with Ewing sarcoma.[3–7] However, in prospective multi-institutional trials for relapsed Ewing sarcoma, the response rate for 80 total patients was only 12%.[8,9] In the one study involving newly diagnosed patients with Ewing sarcoma, two cycles of GEM/DOC were used as an upfront window to treat 17 evaluable higher-risk patients.[10] Although 41% of patients had a partial response, 29% experienced progression during this window. All patients then received five-drug chemotherapy as per the modified P6 protocol[11] followed by local control with surgery and/or radiotherapy. Nonprogressing patients were given up to 12 cycles of GEM/DOC maintenance therapy, and the three-year event-free survival for this group was 29%. These findings suggest that the regimen may have some activity, but modifications to improve activity could strengthen the rationale for incorporation into the care of newly diagnosed patients.

Advances in nanotechnology have allowed insoluble hydrophobic agents such as paclitaxel to be encapsulated with albumin nanoparticles, creating the compound known as nanoparticle albumin-bound (nab)-paclitaxel. This strategy improves drug exposures, reduces infusion reactions, and increases intracellular accumulation of drug in animal models.[12] Drug delivery is facilitated by the albumin nanoparticle binding to the endothelial cell receptor gp60, which induces caveolin-1 (CAV-1) to assist with internalization of drug into calveolae with subsequent release into the interstitial space.[12] Once there, nab-paclitaxel enters the tumor cell through binding secreted protein, acidic, and rich in cysteine (SPARC).[13]

The Pediatric Preclinical Testing Program showed nab-paclitaxel produced complete responses in five of eight Ewing sarcoma mouse models tested,[14] and a recent phase I/II study of single-agent nab-paclitaxel reported one complete and one partial response in patients with relapsed Ewing sarcoma.[15] Further, nab-paclitaxel also has additive *in vivo* activity with gemcitabine against a Ewing sarcoma xenograft model,[16] and this combination is approved by the US Food and Drug Administration for treatment of pancreatic cancer. For that disease, gemcitabine 1000 mg/m^2 is given with nab-paclitaxel 125 mg/m^2 once weekly × 3 weeks in 28-day cycles.[17] In our study, we chose to use the same dosages and schedule of administration as approved for pancreatic cancer, given the relative tolerability of this regimen in adults,[17] previous observations that nab-paclitaxel is less myelosuppressive than docetaxel,[18] and the potential activity against Ewing sarcoma of nab-paclitaxel alone and in combination with gemcitabine. To explore the hypothesis that nab-paclitaxel may be a superior taxane to partner with gemcitabine, we conducted a phase II study of this regimen using a Simon's two-staged design to try to identify a response rate of ≥ 35% in patients with relapsed Ewing sarcoma.

2 | METHODS

2.1 | Patient eligibility

This trial studied patients aged 12–30 years with relapsed or refractory Ewing sarcoma following standard front-line therapy. Additional eligibility criteria included having measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[19]

Karnofsky or Lansky score ≥ 60, and recovery from prior therapy as defined by > 3 weeks since myelosuppressive therapy, > 7 days since filgrastim and > 14 days since pegfilgrastim, > 7 days since biological agent, > 3 half-lives for monoclonal antibodies, ≥2 weeks since completion of local palliative radiation, ≥3 months if prior 50% pelvic irradiation, and ≥6 weeks for other substantial marrow irradiation. Patients were required to have adequate bone marrow function (absolute neutrophil count ≥1,000/μL and platelet count ≥100,000/μL), normal serum creatinine or a creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above normal, and bilirubin/AST/ALT ≤ 2.5× upper limit of normal. Patients with medical or social situations that would limit compliance with study requirements were excluded. The Institutional Review Board for each participating institution approved the protocol, and written informed consent and assent (as appropriate) were obtained according to local institutional guidelines.

2.2 | Drug administration

Patients were to receive both nab-paclitaxel and gemcitabine on days 1, 8, and 15. Following premedication with an antiemetic agent as per individual institutional standard guidelines, nab-paclitaxel was given as a 30-minute infusion at the dose of 125 mg/m^2. This was immediately followed by gemcitabine 1,000 mg/m^2, given as a 90-minute infusion. Initially patients did not receive prophylactic myeloid growth factor; however, the protocol was amended after the fourth patient so that all subsequent participants received pegfilgrastim beginning on days 16–18 of each cycle. As with pancreatic cancer studies,[17] both chemotherapy agents were held on day 15 if the patient experienced grade 4 neutropenia on or prior to that day and resumed at a reduced dose with subsequent cycles. Nab-paclitaxel was held for the remainder of the cycle for any patients who experienced grade ≥3 neuropathy. Patients experiencing febrile neutropenia, failure to meet eligibility criteria on day 29, platelets < 20 000 on two occasions during a cycle, or need for two platelet transfusions within a seven-day period were subject to dose reduction of gemcitabine (to 675 mg/m^2) and nab-paclitaxel (to 100 mg/m^2) with subsequent cycles.

2.3 | Toxicity

Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (http://ctep.cancer.gov), and any patient receiving at least one dose of either study drug was considered evaluable for toxicity. Patients who experienced the same dose-modifying toxicities even after the appropriate dose reductions, or who did not meet eligibility criteria to start subsequent cycles by day 43, were withdrawn from protocol therapy.

2.4 | Efficacy

Disease evaluations with cross-sectional imaging were performed within 28 days prior to the start of study, and at the completion of cycle 2. Patients with stable disease or better continued to have evaluations completed at the end of each even numbered cycle.

Tumor response was reported using RECIST 1.1, including the requirement that responses must be confirmed with additional imaging no sooner than 4 weeks. Any patient receiving at least one dose of nab-paclitaxel and gemcitabine was considered evaluable for response

provided: (1) the patient demonstrated progressive disease or death while on protocol therapy; (2) the patient was observed on protocol therapy for at least one cycle and the tumor was not removed surgically prior to the time complete response or partial response is confirmed; or (3) the patient demonstrated a complete or partial response according to protocol criteria. This definition excluded patients who stop therapy because of toxicity before the first disease evaluation (none), and such patients would have been replaced for the purpose of assessing the primary objective of the study.

2.5 | Immunohistochemistry

Based on the mechanism of nab-paclitaxel cell entry, protein expression of CAV-1 and SPARC are putative biomarkers for activity of this drug.[20–22] Similarly, human equilibrative nucleoside transporter-1 (hENT-1) facilitates transport of gemcitabine into cells, and its expression has correlated with gemcitabine response in patients with soft-tissue sarcoma.[23] We performed immunohistochemistry on the most recent archived tumor tissue available. Three commercially available antibodies were optimized and tested to select the most appropriate one for assay development: SPARC (Clone: sc-73472, dilution 1:50, Santa Cruz Biotechnology), Caveolin-1 (Clone: 7C8, dilution 1:20, Thermo Fisher Scientific), and ENT1 (Clone: SP120, no dilution, Abcam).

To quantify protein expression, we used an immunoreactivity score system that incorporates the relative percentage of tumor cells expressing the protein, as well as the relative intensity of staining.[24] The score for proportion of tumor cells ranged from 0 to 4 and was based on the proportion of tumor cells expressing the marker (0 = none, 1 ≤ 10%, 2 = 10%−50%, 3 = 51%−80%, and 4 ≥ 80%). The intensity of staining was scored from 0 to 3 and based on the relative extent of color change noted (0 = none, 1 = mild, 2 = moderate, and 3 = dark brown). The immunoreactivity score was the product of these two scores, and scores of 0–1 were considered negative expression, 2–3 were mild, 4–8 were moderate, and 9–12 were termed strong expression.

2.6 | Statistical analysis

The primary objective of this study was to determine the objective response rate to the drug combination in patients with relapsed or refractory Ewing sarcoma. A Simon's two-staged design was used in which the null hypothesis that the true response rate was ≤ 10% was tested against a one-sided alternative response rate of ≥ 35%. This target response rate was chosen because this level of activity has been achieved by other available salvage regimens[1] and has been used for cooperative group studies in recurrent Ewing sarcoma.[25] Eleven evaluable patients were accrued in the first stage. If two or more confirmed responses using RECIST 1.1 criteria were seen in this group, then seven additional patients would be added in a second stage for a total of 18 patients. The null hypothesis would be rejected if five or more responses were seen in 18 patients. This design yields a type 1 error rate of 0.027 and power of 0.80 when the true response rate is 35%. Estimation of progression-free survival (PFS) was completed using Kaplan-Meier methods with confidence interval based on the log-log approach, where progression was determined based on RECIST1.1.

3 | RESULTS

Eleven patients with histologically confirmed Ewing sarcoma were enrolled between October 2016 and August 2018 across four sites. Eight patients had molecular testing of tumor tissue showing either rearrangements or specific translocations involving *EWSR1*, while three patients did not have molecular testing reported. All 11 patients were evaluable for toxicity and for disease response. The median age was 22 years (range, 14–27 years), and the patient characteristics are detailed in Table 1. Of note, patients were heavily pretreated, with a median of three prior lines of therapy (range, 1–7). Regarding prior salvage regimens, seven had received irinotecan and seven topotecan.

Thirty-five treatment cycles were administered, with a median of two cycles and a range of 1–8. All patients received gemcitabine and nab-paclitaxel until disease progression or until toxicity required discontinuation as defined by the physician, patient, or protocol. No patient received additional anticancer therapy while on study.

3.1 | Toxicity

Grade 3–4 toxicities are listed in Table 2. The predominant adverse effect was myelosuppression, with 55% of first cycles complicated by grade 3–4 neutropenia, thrombocytopenia, or infection. In total, eight (73%) of 11 patients had dose reductions and/or missed doses due to toxicity, including four of seven patients with dose-modifying hematologic toxicity or infection despite use of prophylactic pegfilgrastim. A total of 4 (36%) patients were removed from protocol therapy for recurrent myelosuppression despite reducing doses of gemcitabine and nab-paclitaxel to 675 mg/m^2 and 100 mg/m^2, respectively. Five patients were hospitalized with treatment-related toxicities, including nonneutropenic fever (3), febrile neutropenia (1), and cellulitis. Additional grade 3 toxicities included myalgia, dehydration, transaminase elevation, and fatigue. There were no grade 4 nonhematologic toxicities, and no patient died from treatment-related toxicity.

3.2 | Responses

Only one patient had a partial response that was confirmed on subsequent imaging, and thus met the RECIST v1.1 criteria for an objective response. This patient had a 91% reduction in cumulative RECIST measurements of intrathoracic tumor and went on to receive eight cycles before progression was documented. Two other patients had evidence of a partial response on imaging conducted after cycle 2, but these patients subsequently withdrew before the response could be confirmed on follow-up imaging because of nontarget disease progression or hematologic toxicity. Therefore, per RECIST v1.1 criteria, only one patient was considered to have a confirmed response, and so accrual was not expanded beyond the initial 11 patients in stage 1 of the Simon's two-stage design. The median PFS for this cohort of patients was 4.8 months, and the six-month PFS was 40% (95% confidence interval of 7%−72%).

Table 3 details the relationship of toxicity, dose modification, imaging response, and number of prior treatment regimens. Three of 11 patients had no modifications in dose or schedule throughout eight cumulative cycles. The remainder underwent some type of dose

modification, almost always due to hematologic toxicity. In this small cohort, there was no clear relationship identified between toxicity and number of prior regimens or response.

3.3 | Immunohistochemistry

Seven of 11 patients had archival tissue available for immunohistochemical analysis of hENT1, as detailed in Table 4. The small numbers preclude a statistical assessment of results, and so results from this study are purely descriptive. It is noted that two of the three patients who received three or more cycles had expression of hENT1 in archival tumor, with none of the other patients demonstrating this finding.

4 | DISCUSSION

In this prospective multi-institutional trial, we did not observe a sufficient number of sustained objective responses by RECIST v1.1 to expand accrual using the Simon's two-stage design to identify a response rate of ≥ 35%. Only one of 11 evaluable patients achieved a response that was confirmed on follow-up imaging, and this persisted through eight cycles. Two other patients had partial responses after two cycles but came off study due to disease progression or hematologic toxicity before the response could be confirmed with subsequent imaging. This objective response rate of 9% is similar to that seen in prospective multi-institutional studies of GEM/DOC in this patient population.[8,9]

It was anticipated that myelosuppression would be dose limiting for this regimen, and in fact a previous retrospective report by Metts et al. of the use of gemcitabine and nab-paclitaxel showed that 5 (38%) of the 13 patients with recurrent pediatric sarcoma treated on this same schedule experienced grade 4 neutropenia.[26] In our study of 11 patients, 55% of patients had grade 4 neutropenia and 64% required dose reductions using the standard treatment recommendations used for pancreatic cancer.[17] Hematologic toxicity resulted in 36% of patients in our study being removed even after dose reductions. Factors contributing to this toxicity may include the extensive pretreatment of our patients, and perhaps the relatively older median patient age compared with the Metts study (22 years for our study vs 13 years).[26] In addition, we administered gemcitabine over 90 minutes, and this longer infusion rate has been associated with greater myelosuppression compared with the 30-minute schedule used for pancreatic cancer.[27] Because the primary objective of the study was to determine the activity of the combination for recurrent Ewing sarcoma, we purposefully chose the longer infusion schedule, which may result in higher plasma and intracellular levels of active metabolites and potentially improved antitumor activity.[27–30] In fact, while the Metts study used a 60-minute gemcitabine infusion, most other sarcoma studies have given this drug over 90 minutes.[2,7–9] Finally, alternative administration schedules may possibly reduce hematologic toxicity,[31] and are being explored as part of our ongoing assessment of this drug combination in other types of pediatric sarcoma (clinicaltrials.gov identifier NCT02945800).

Because this regimen has toxicity but only limited activity, identification of predictive biomarkers would be quite helpful for patient selection. Previous studies suggested that expression of either SPARC or CAV-1 in archival tumor samples may correlate with response to nab-paclitaxel,[20–22] which fits with the presumed method of drug entry into the

tumor cell. However, not all studies confirm this association between SPARC expression and response to nab-paclitaxel,[32] and it is possible that the predictive value of the marker may depend on tumor type or expression in stroma versus tumor cells.[33] Our study was limited in that only seven patients had archival samples suitable for review, and no associations were identified between response and expression of either SPARC or CAV-1. Interestingly, the expression of hENT1 in tumor cells was limited to those patients experiencing clinical benefit on our study, which is consistent with expression of hENT1 being associated with sensitivity to gemcitabine in soft-tissue sarcoma patients.[23] Testing of additional samples from the ongoing larger trial of this combination referenced above may help clarify potential relationships between biomarker expression and response.

In summary, this phase II trial of gemcitabine and nab-paclitaxel showed limited sustained activity in a heavily pretreated population of mostly young adults with multiply recurrent Ewing sarcoma. In fact, the study response rate of 9% was similar to that of the largest prospective study of GEM/DOC in patients with recurrent Ewing sarcoma. Although comparison across studies is problematic, there is no suggestion to date that the combination given on this schedule improved the response rate when compared with GEM/DOC for patients with recurrent Ewing sarcoma. The potential benefit of this combination in other types of relapsed pediatric sarcoma, as well as a more comprehensive assessment of toxicity and tissue biomarkers, is being assessed in an ongoing study.

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Abbreviations:

CAV-1	caveolin-1
GEM/DOC	gemcitabine and docetaxel
hENT-1	Human equilibrative nucleoside transporter-1
RECIST	Response Evaluation Criteria in Solid Tumors
SPARC	secreted protein, acidic and rich in cysteine

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TABLE 1

Patient characteristics

Median age (range)	22 years (14–27)
Gender (M:F)	5:6
Prior number of regimens	Median 3
1	1
2	2
3	4
4	2
5 or more	2
Prior radiotherapy	10
Site of measurable disease	
Intrathoracic disease only	6
Bone with soft-tissue component	3
Intrathoracic disease plus additional sites	2

TABLE 2

Number of patients with grade 3–4 toxicities attributable to study therapy

	Cycle1 (*n* = 11 patients)		Subsequent cycles (*n* = 9 patients)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Neutropenia	2	5	3	1
Thrombocytopenia	3	2	3	3
Lymphopenia	2		2	
Anemia	5		5	
Fever	3			
Febrile neutropenia	1			1
Cellulitis	1			
Dehydration	1			
Dyspnea	1			
Fatigue			1	
Myalgia	1			
ALT elevation	1		1	
Motor neuropathy			1	

TABLE 3

Relationship of toxicities, dose reductions, prior treatments, and response

Age	Cycles	Dose modified	Off treatment reason	RECIST response	Prior regimens
24	2	No	PD	PD	2
21	2	Yes (Cy 1)	Toxicity	PD	2
18	1	No	PD	PD	3
14	1	Yes (Cy 2)	PD	PD	3
27	6	Yes (Cy 6)	Withdrew	SD	3
26	3	Yes (Cy 2)	Withdrew	SD	6
22	3	Yes (Cy 1)	Toxicity	SD	1
17	2	Yes (Cy 1)	Toxicity	SD	4
25	5	No	PD	Unconfirmed PR	4
21	2	Yes (Cy 1)	Toxicity	Unconfirmed PR	7
23	8	Yes (Cy8)	PD	Confirmed PR	3

Cy, cycle; PD, progressive disease; SD, stable disease.

TABLE 4

Immunoreactivity scores of putative biomarkers from patients with available tissue correlated with response to therapy

hENT1	CAV-1	SPARC	Cycles received	Best response
Neg	Mod	Strong	2	PD
Neg	Neg	Strong	1	PD
Neg	Neg	Neg	2	PD
Neg	Mod	Neg	1	PD
Patients with clinical benefit				
Mod	Strong	Mild	8	PR
Mild	Mod	Mod	5	PD
Neg	Mod	Strong	3	SD

Mod, moderate; Neg, negative; PD, progressive disease; PR, partial response; SD, stable disease.