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The use of interval-compressed chemotherapy with the addition of vincristine, irinotecan and temozolomide for pediatric patients with newly diagnosed desmoplastic small round cell tumor

Kevin X. Liu[1], **Natalie B. Collins**[2], **Katie A. Greenzang**[2], **Elissa Furutani**[2], **Kevin Campbell**[2], **Andrew Groves**[2], **Elizabeth A. Mullen**[2], **Suzanne Shusterman**[2], **Jennifer Spidle**[2], **Karen J. Marcus**[1], **Brent R. Weil**[3], **Christopher B. Weldon**[3], **A. Lindsay Frazier**[2], **Katherine A. Janeway**[2], **Allison F. O'Neill**[2], **Jennifer W. Mack**[2], **Steven G. DuBois**[2], **David S. Shulman**[2]

[1]Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts.

[2]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, Massachusetts.

[3]Departments of Surgery, Anesthesiology& Pediatric Oncology, Boston Children's Hospital/Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

Abstract

Background: Desmoplastic small round cell tumor (DSRCT) is a rare aggressive sarcoma that affects children and young adults and portends poor outcomes despite intensive multimodal treatment approaches. We reporttoxicity, response and outcomes of patients with DSRCT treated with the addition of vincristine, irinotecan, and temozolomide (VIT) to interval-compressed chemotherapy as per Children's Oncology GroupARST08P1.

Methods: All newly diagnosed pediatric patients with DSRCT treated at Dana-Farber Cancer Institute and Boston Children's Hospital between 2014 and 2019as per ARST08P1, Arm P2 with replacement of VAC cycles with VIT, were identified.Medical records were reviewed for clinical and disease characteristics, and treatment response and outcomes.

Results: Six patients were treated as per the above regimen. Median age at diagnosis was15.1 years (range: 3.2-16.4) and five patients were male. Five patients had abdominal primary tumors, of which one had exclusivelyintra-abdominal and four hadextra-abdominal metastases. Two initial cycles of VIT were well tolerated with nausea, vomiting, diarrhea, and constipation as the most common adverse events. Overall response rate defined as partial or complete response after two initial cycles of VIT was 50%. For local control, all patients had surgical resection followed by radiotherapy, and two patients received hyperthemic intraperitoneal chemotherapy at the time of

Corresponding Author: David S. Shulman, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. Phone: (617) 632-6670, David_Shulman@dfci.harvard.edu.

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DATA SHARING: The data that support the findings of this study are available in a limited format on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

surgery. Of the four patients who have completed therapy to date, three remain disease-free with median follow-up time of 46.7 months.

Conclusions: Theaddition of VIT to interval-compressed chemotherapy is tolerable and active in DSRCT, with activity warranting additional investigation.

Keywords

desmoplastic small round cell tumor; sarcoma; pediatric; adolescent; radiation; chemotherapy; ARST08P1

1. INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare aggressive sarcoma affecting children and young adults. These tumors are defined by a translocation between the *EWSR1* and *WT1* genes.[1]Patientsoften present with a primary abdominal mass with diffuse intra-abdominal dissemination. Reported long-term outcomes areexceedingly poor with five-year overall survival (OS) rates of approximately 20%.[2-11]Current multimodal therapeutic approaches consist of intensive multi-agent chemotherapy and local control measures including surgery and whole abdomen radiotherapy (WART) with or without hyperthermic intraperitoneal chemotherapy (HIPEC). Aggressive local control with surgery and WART have been shown to be associated with improvements in overall survival.[2-9,11,12]

While multi-agent chemotherapy is also thought to be important for achieving long-term survival,an optimal regimen remains undetermined.[3,4,7]A wide range of chemotherapy regimens have been utilized for DSRCT, often based on treatment strategies for Ewing sarcoma.[3,4]Responses to vincristine and irinotecan in DSRCT have been reported in the published literature, and this combination is active in many sarcomas.[13-18] Temozolomide has also been of interest in DSRCT given its radiosensitizing effects.[8]

The Children's Oncology Group (COG) protocol ARST08P1, which was initially developed for children with high-risk rhabdomyosarcoma, evaluated interval-compressed vincristine/doxorubicin/cyclophosphamide (VDC) alternating with cycles of ifosfamide/etoposide (IE), cycles of vincristine/dactinomycin/cyclophosphamide (VAC) and either cycles of vincristine/irinotecan/temozolomide (VIT, Arm P2) or vincristine/irinotecan/cixutumumab (arm P1).[19] This regimen was tolerable, but did not improve outcomes for patient with high-risk rhabdomyosarcoma.[19]Given the known efficacy of many of these agents in DSRCT, this regimen, utilizing the temozolomide-containing arm P2 withsubstitution of VAC for VIT cycles given lack of evidence for the use of dactinomycin in DSRCT, became the standard initial treatment regimen at our center in 2014. The tolerability and efficacy of Arm P2 when given in combination with the aggressive local control strategies utilized in DSRCT remains unknown.Herein, we describe a case series of pediatric patients with DSRCT and report clinical outcomes for patients receiving modified intensive multi-agent interval compressed chemotherapy as per ARST08P1 with VIT.

2. METHODS

Thisstudy was deemed exempt by the Dana-Farber Cancer Institute Institutional Review Board. We performed a retrospective chart review of pediatric patients diagnosed with DSRCT and treated as per ARST08P1 prior to Nov 1, 2019 at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. We report all six cases, who represent the most recent six consecutive patients to present to our center with newly diagnosed DSRCT. EWSR1-WT1 translocation was confirmed in all cases. Cycles containing dactinomycin were replaced with VIT and the modified treatment regimen as per ARST08P1 can be found in Supplemental Figure 1.

For each patient, we performed medical record reviews and extracted demographic, disease-related, treatment-related and outcome data, including age, sex, race, ethnicity, presentation, pathology, treatment course, acute and late toxicity, disease and survival status, and clinical follow-up. Imaging was reviewed, and response to two cycles of VIT and best overall response was assessed by two physicians according to RECIST 1.1 criteria for solid tumors.[20] Overall response rate after induction chemotherapy with two cycles of VIT was defined as the proportion of patients with complete or partial response as defined by RECIST 1.1 criteria for solid tumors.[20] Surgical resection status was determined using the residual tumor (R) classification where R0 is defined as resection with no cancer cells seen microscopically at the resection margins of the primary tumor bed and R1 is defined as resection with cancer cells present microscopically at the margins of the primary tumor bed.[21] Progression-free survival (PFS) was defined as the time from the date of initial diagnosis to the date of last follow-up time or progression of DSRCT. OS was defined as the time from the date of initial diagnosis to the date of last follow-up or death. Disease and patient characteristics, toxicity and outcomes were reported descriptively.

3. RESULTS

3.1 Clinical characteristics

Clinical and treatment characteristics are summarized in Table 1.Median age at diagnosis was 15.1 years (range: 3.2-16.4). Four patients (66.7%) presented with abdominal or flank pain. The median size of the largest tumor deposit was 10.25 cm (range: 4.6-13.5; Figure 1A,C,E). Four patients had extra-abdominal lymph node involvement and one had liver parenchymal metastaseswithout involvement of the porta hepatis at presentation.One patient had a primary tumor arising outside of the abdomen and pelvis. All patients had evidence of an EWSR1-WT1 translocation identified by FISH, RT-PCR or next-generation sequencing.

3.2 Response to induction chemotherapy with two initial cycles of VIT

All six patients received two induction cycles of VIT followed by re-staging scans. The overall response rate was 50% with three patients having a partial response and three patients having stable disease (Figures 1-2). Patients tolerated the first two cycles of VIT well. Common symptoms were nausea, vomiting, constipation, and diarrhea.No patients were admitted for febrile neutropenia. Notably, one patient developed severe *C. difficile*

colitis requiring intensive care unit admission during cycle 3 of chemotherapy, and had no prior use of proton pump inhibitors.

3.4 Treatment Outcomes

Of the six patients, two are actively still undergoing frontline treatment. Patient 5 has completed 8 neoadjuvant cycles of chemotherapy, surgical resection, WART, and 7 adjuvant cycles.Patient 6 has completed 5 neoadjuvant cycles of chemotherapy, surgical resection, 2 adjuvant cycles, and is undergoing chemoradiation to the primary site. Of the four patients who completed therapy, three remain disease-free at a median follow-up of 46.7 months (range: 20.7-60.3) (Table 2).Despite a 48.1% reduction in tumor burden per RECIST criteria after two initial cycles of VIT (Figure 2A) and an eventual complete response, patient 1 had liver metastases at diagnosis experienced distant relapse five months after completing therapy and ultimately died due to disease at 19.3 months from diagnosis. Two-year PFS and OS for the cohort are 75.0%.

At the end of neoadjuvant chemotherapy, all patients achieved a partial response (Figure 2B). The patients received a median of 6.5 neoadjuvant chemotherapy cycles (range: 5-9) followed by complete cytoreductive surgery (Table 2).All patients had surgical pathology showing residual viable tumor at time of surgical resection, and all patients had ≤30% tumor necrosis noted in the primary tumor. Interestingly, Patient 6 had 100% tumor necrosis in the involved lymph node after five neoadjuvant chemotherapy cycles.No patients had macroscopic residual disease after complete cytoreductive surgery.An R0 resection was achieved in two patients (33.3%) and R1 resection was achieved in four patients (66.7%) (Table 2). Two patients received HIPEC after surgical resectionwith complete cytoreduction as previously described.[2]Following post-operative recovery, all patients received consolidation with concurrent chemoradiationwith median total dose of 42.9 Gy (range: 24-55.8) (Table 2). For the five patients with intra-abdominal primary tumors, all received WART (median dose: 30 Gy, range: 19.5-30) with three patients receiving concurrent VIT, one patient with VIT/IE, and one patient with VDC/IE (Table 2). For Patient 3, doxorubicin was given prior to the start of radiation. Three patients received pelvic boost radiotherapy (median dose: 14.4 Gy, range: 14.4-21.9) given large burden of pelvic disease prior to surgery, and of these three patients receiving a radiation boost to the pelvis, two had R1 resections(Table 2).Patient 2 received a simultaneous integrated boost to her extra-abdominal lymph nodes for a total dose of 36 Gy.Due to his young age, Patient 4 received 19.5 Gy of WART followed by a 21.9 Gy pelvic boost.Because all patients underwent an R0 or R1 resection, no patients received boost radiotherapy for gross residual disease.Patient 6 is planned to receive concurrent chemoradiationwith a total dose of 55.8 Gy to his inguinal primary and lymph node (Table 2). Of the four patients who completed therapy, the median number of adjuvant chemotherapy cycles was 10.5 (range: 5-15) with replacement of dactinomycin-containing cycles with VIT cycles, and all patients achieved complete responses (Table 2).

The most common side effects throughout treatment, including the initial two cycles of VIT,were nausea, vomiting, diarrhea, constipation, myelosuppression requiring red blood cell or platelet transfusions, febrile neutropenia, and *C. difficile* infection. For irinotecan-

associated diarrhea, patients received oral cephalosporin prophylaxis.[22,23]Only one of three patients who developed *C. difficile* infections had prior use of proton pump inhibitors before diagnosis of infection. Patients 1 and 2received HIPEC and had gastrointestinal toxicity during and after consolidation chemoradiation and adjuvant chemotherapy (Table 2). Due to complications with small bowel obstruction requiring exploratory laparotomy and lysis of adhesions, post-operative wound infection, intussusception, functional ileus, and C. difficile infection, Patient 1 only completed 5 adjuvant cycles following HIPEC and WART for a total of 14 cycles, and suffered a relapse five months after completion of therapy. Patient 2 completed WART, 20 planned cycles of therapy, andrequired prolonged gastrostomy-jejunostomy tube feeding with poor nutrition. She had delay of adjuvant cycles due to chylous ascites of unclear etiology, which ultimately resolved with diet modification. After completion of therapy, she underwent lysis of adhesions for partial small bowel obstruction with improvement of symptoms, butdeveloped an enterocutaneous fistula that resolved with non-operative management. She remains disease-free at 46.7 months. Patient 3 developed sinusoidal obstruction syndrome (SOS) requiring defibrotide and a peritoneal drain during concurrent WART with VIT. Radiation was stopped early at 24 Gy of the 30 Gy planned treatments, and chemotherapy was stopped early at 14 total cycles due to SOS and *C. difficile* infection. He was subsequently transitioned to and completed maintenance pazopanib for six planned cycles.The patient remains disease-free at 20.7 months of follow-up from diagnosis. Patient 4 was unique in their young age at diagnosis(3.2 years), completed all treatment and isdisease-free more than 5 years from diagnosis (Table 2).

4. DISCUSSION

This report provides the first case series of patients with DSRCT receiving VIT in addition to interval-compressed chemotherapy as per COG ARST08P1. We report an overall response rate of 50%after two induction cycles of VIT, and three of four patients who completed treatment as per ARST08P1 are without evidence of disease at median follow-up of 46.7 months. Our data suggest that the addition of VIT to an interval compressed VDC/IE backboneistolerable, albeit with notable toxicity when combining the full regimen with extensive local control measures,anddemonstrates a level of activity warranting further evaluation.

Our cohort included five male patients (83.3%), which is similar to the previously reported rates of male predilection of approximately 4:1 in DSRCT.[5,10]Abdominal pain was the most frequent presenting symptom. One patient had an extraabdominal primary tumor, which is uncommon.[24]In our cohort, no patients had bone metastases at diagnosis, which is a rare occurrence in the literature.[10] Four patients had enlarged extraabdominal lymph nodes at the time of diagnosis. We reported one patient (16.7%) with liver metastases at the time of diagnosis, which is similar to the reported frequency for liver metastases in patients with DSRCT.[10]The patient with metastatic disease to the liver on presentation had distant recurrence five months after completing therapy and ultimately died due to his disease. Liver metastases have been previously associated with poor prognosis.[2,6,18] Furthermore, data suggest that despite aggressive local therapy, including complete resection, HIPEC, and WART, patients with liver metastases have poor prognosis.[2]

While response to vincristine, irinotecan, and temozolomide has been reported in DSRCT, [8,13-18]use of all three agents has not been described for this disease in combination with interval-compressed therapy in the upfront setting. We found that that VIT has activity against DSRCT, andin our cohort no patients experienced disease progression while on therapy.This treatment strategy of initiating therapy with VIT may be particularly useful for patients presenting with extensive abdominal disease who may have difficulty tolerating initial cycles of VDC/IE. Furthermore, allpatients completed neoadjuvant chemotherapy witha partial response.In comparison, in one large cohort of patients receiving varied regimens (interval-compressed VDC/IE, standard VDC/IE, vincristine/ifosfamide/ doxorubicin/etoposide [VIDE], vincristine/ifosfamide/dactinomycin [VIA] or P6), 51.9% of patients had a partial response or better prior to local control, and this was associated with improved outcomes.[12]Although the study was not powered to assess differences in response by chemotherapy regimen, response rates for interval-compressed VDC/IE and standard VDC/IE were 68.4% and 48.2%, respectively.[12]The P6 protocol from Memorial Sloan Kettering consists of cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide and etoposide,and the initial report found 100% response rate in 10 patients who received P6 as first-line therapy.[3] Additionalstudies with larger cohorts using neoadjuvant P6 have not reported exact response rates;[6,25,26] however, Lal et al. reported that a majority of patients in a subsequent update study had a good response to 3-4 cycles of chemotherapy, consisting of P6 protocol with addition of irinotecan, topotecan, carboplatin and cisplatin for selected patients.[4]Preliminary results from a new pilot study exploring the addition of induction irinotecan, temozolomide and bevacizumab (ITB) to a modified P6 regimen found response rates of 27% following an initial two cycles of ITB and 73% at the completion of five neoadjuvant chemotherapy cycles.[27]Furthermore, all patientsin our study underwent an R0/R1 surgical resection after neoadjuvant chemotherapy with VIT, and results from a recent abstract demonstrated achievement of R0/R1 resection to be a predictor of overall survival.[28]

After neoadjuvant chemotherapy, all patients went on to undergo complete cytoreductive surgery followed by concurrent chemoradiation with five patients receiving WART for intra-abdominal primary tumors and one planned to receive radiation to his extra-abdominal primary tumor and lymph node. Four patients were planned for 30 Gy of WART, which is a commonly used dose for WART in DSRCT,[4,7,8] and only 1 patient was unable to complete the planned radiation treatment due to SOS, receiving only 24 Gy. Patient 4 was 3.2 years old at diagnosis, and given the young age, received 19.5 Gy WART, a dose previously used for patients with Wilms tumor and extracranial rhabdoid tumors.[29,30]Four of five patients with intra-abdominal primary tumors received at least one cycle of VIT during radiation treatment. A previous study exploring the radiosensitizing effects of irinotecan and temozolomide in DSRCT and described a patient who is without disease 20 months after completion of WART with concurrent irinotecan/temozolomide.[8]It is possible that theradiosensitizing properties of VIT when used concurrently with radiotherapy may also contribute to better local control. Given the small number of patients, it is difficult to determine whether WART or total radiation dose impacted disease outcomes.For patients with DSRCT, relapses most frequently occur in the first two years after diagnosis.[2,5,6,10]In

our case series, two patients who completed 20 cycles of planned chemotherapy are disease-free at 46.7 and 60.3 months.

The first two cycles of VIT were generally well-tolerated. During neoadjuvant therapy, the most common side-effects were gastrointestinal and hematologic and did not result in significant treatment delays. Three patients developed *C. difficile* colitis with two patients developing this infection during adjuvant treatment, a side-effect previously described during VDC/IE or irinotecan/temozolomide for pediatric sarcomas.[31,32] While proton pump inhibitors have been associated with increased risk of *C. difficile* infection,[33] only one patient had prior use of proton pump inhibitors. However, cephalosporin prophylaxis of irinotecan-associated diarrhea may have been a contributing factor as cephalosporins have been associated with *C. difficile* infections.[34]Toxicity following extensive local control measures and adjuvant chemotherapy were more profound and included small bowel obstruction, prolonged gastrostomy-jejunostomy tube requirement, enterocutaneous fistula, and SOS. Thesetoxicities were similar to those previously reported using other chemotherapy regimens and extensive local surgery, HIPEC, and WART.[2-4,6,7,35]In this setting, these toxicities precludedsome patients from completing planned adjuvant chemotherapy regardless of whether HIPEC was utilized.There have been few studies examining the association of WART dose with toxicity; however, studies have found higher doses of radiation to the abdomen and pelvis correlates with greater long-term toxicity.[36,37] Future studies are needed to understand the optimal WART dose for patients with DSRCT that balance toxicity with achieving disease control.In one instance, maintenance pazopanib was added for a patient with toxicity that prevented completion of planned cycles. Taken together, these findings suggest that the addition of VIT to interval compressed chemotherapyas per ARST08P1 is tolerable in this disease context.However, toxicity for the entire regimen, particularly following the extensive local control strategies utilized in this disease, are profound in comparison to those seen among patients with rhabdomyosarcoma treated with similar regimens (ARST08P1 and ARST0431) and may preclude completion of all planned cycles.[19,38] Given these serious toxicities, striving to better understand the relative importance of aggressive local control and the need to complete all planned cycles of adjuvant chemotherapy in order to maximize the chances of long-term survival will be an important area for future study.

One patient who developed complications during adjuvant chemotherapy cycles was transitioned to six planned cycles of pazopanib, and is currently without evidence of disease at 20.7 months from initial diagnosis. Studies have demonstrated that pazopanib is active in DSRCT and well-tolerated.[39,40] It remains unknown whether patients with DSRCT benefit from targeted agents, such as pazopanib in the upfront setting, or whether maintenance therapy may be beneficial. Further studies are needed to investigate the role of maintenance therapy, potentially with pazopanib, as part of first-line treatment for DSRCT.

There are several limitations to this study. As a small retrospective study, we are unable to make definitive claims about tolerability orefficacy. Similarly, we do not present a direct comparator group, but instead utilize historic controls. Nevertheless, we report all patients at our center with this very rare disease who were treated with a uniform chemotherapy regimen. Furthermore, other factors, such as extent of disease at presentation, may also

confound our results as liver metastases or extra-abdominal involvement are known to influence outcomes.[6]Of note, two of six patients remain on therapy with 4.4 and 10.1 months follow-up from initial diagnosis.Longer follow-up is also needed as long-term survivors will be at risk of numerous late effects, including infertility; cardiac, genitourinary, and gastrointestinal toxicity; and second malignancies. Future prospective studies with larger cohorts are necessary to further examine the role of VIT in addition to interval-compressed chemotherapy in DSRCT.

In conclusion, DSRCT is a rare aggressive sarcoma with poor outcomes despite intensive multimodality treatment. Our data suggest that the addition of VIT to interval-compressed chemotherapy as per COG ARST08P1 is tolerable with a higher than expected disease control rate. Further prospective studies with larger cohorts are needed to examine the efficacy of treating patients with DSRCT using VIT-containing regimens such as per ARST08P1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

COG	Children's Oncology Group
DSRCT	desmoplastic small round cell tumor
HIPEC	hyperthermic intraperitoneal chemotherapy
IE	ifosfamide/etoposide
ITB	irinotecan/temozolomide/bevacizumab
SOS	sinusoidal obstruction syndrome
VAC	vincristine/dactinomycin/cyclophosphamide
VDC	vincristine/doxorubicin/cyclophosphamide
VIA	vincristine/ifosfamide/dactinomycin
VIDE	vincristine/ifosfamide/doxorubicin/etoposide
VIT	vincristine/irinotecan/temozolomide
WART	whole abdomen radiotherapy

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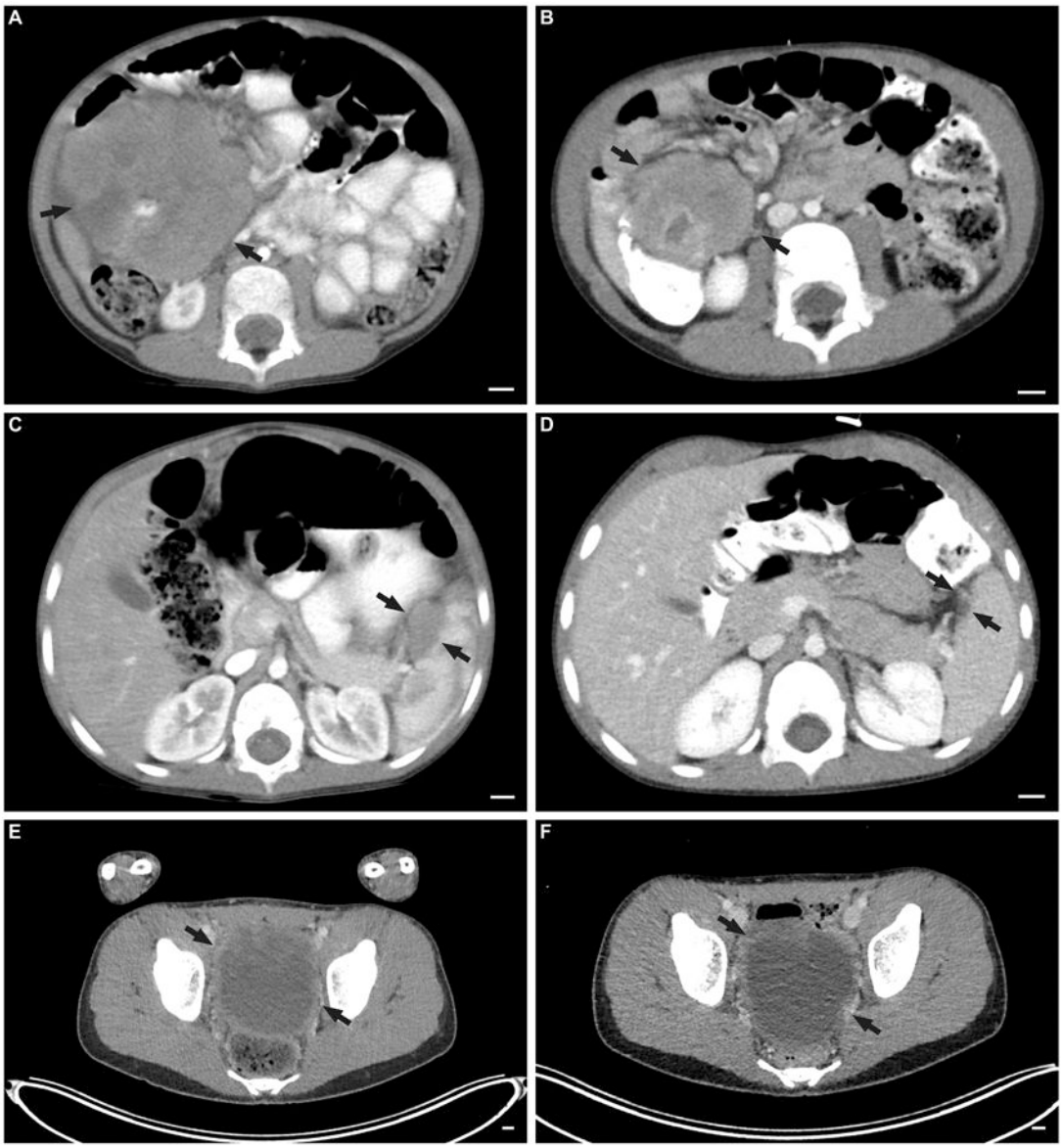

FIGURE 1.

Tumor imaging at diagnosis and after two induction cycles of VIT as per ARST08P1. Representative images of abdominal tumor (A) before and (B) after two cycles of VIT in one of the patients with partial response. Representative images of splenic lesion (C) before and (D) after two cycles of VIT in one of the patients with partial response. Representative images of a large pelvic lesion (E) before and (F) after two cycles of VIT in one of the patients with stable disease.

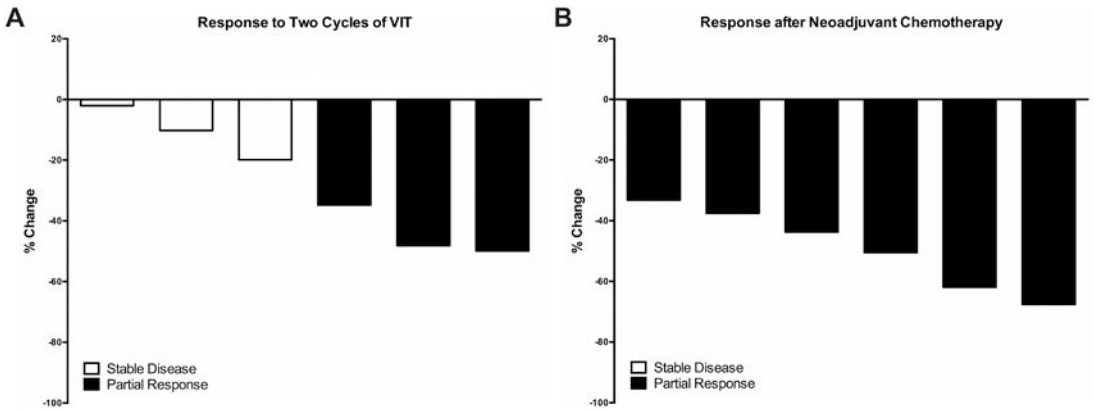

FIGURE 2.

Response during and after neoadjuvant chemotherapy. (A) Percentage of response after two cycles of VIT as measured by RECIST 1.1 criteria for patients receiving chemotherapy as per ARST08P1. (B) Percentage of response after completion of neoadjuvant chemotherapy as measured by RECIST 1.1 criteria for patients receiving chemotherapy as per ARST08P1.

TABLE 1

Clinical and disease characteristics

Patient	Age at diagnosis (years)	Sex	Race/ Ethnicity	Presenting Symptoms	Largest tumor deposit diameter at diagnosis (cm)	Liver metastases at diagnosis	Bone marrow involved at diagnosis	Extra-abdominal sites at diagnosis (locations)
1	9.3	Male	NH White	Abdominal pain	5.7	Yes	No	No
2	15.9	Female	NH Black	Palpable abdominal mass	13.5	No	No	Yes (cardiac apex nodule, IMN)
3	14.5	Male	Hispanic	Abdominal pain	13.5	No	-	Yes (cardiophrenic nodule)
4	3.2	Male	NH White	Abdominal pain, fevers	10.2	No	No	Yes (cardiophrenic nodule, IMN)
5	16.4	Male	NH Black	Flank pain, vomiting, constipation	10.3	No	-	No
6	15.7	Male	Hispanic	Thigh mass, fevers	4.9	No	-	Yes (primary thigh mass, inguinal LN, hilar LN)

Abbreviations: IMN, internal mammary nodes; LN, lymph node; NH, non-Hispanic

TABLE 2

Frontline treatment characteristics and outcomes

Patient	Treatment (in order received)	Response after two cycles of VIT	Best response after frontline therapy	Recurrence (time after treatment completion)	Toxicity	Disease status	Time from diagnosis to last follow-up or death (months)
1	ARST08P1 (VIT, VDC, IE) with 9 NAJ cycles, surgical resection (20% necrosis, R1) with HIPEC, concurrent WART (30 Gy) and pelvic boost RT (14.4 Gy, total dose of 44.4 Gy) with VIT, 5 ADJ cycles	PR	CR	Y (5 months)	Nausea, vomiting, diarrhea, constipation, myelosuppression, *C. difficile* infection, SBO requiring lysis of adhesions, intussusception, ileus, post-operative wound complications	DOD	19.3
2	ARST08P1 (VIT, VDC, IE) with 8 NAJ cycles, surgical resection (<20% necrosis, R1) with HIPEC, concurrent WART (30 Gy)and RT to extra-abdominal nodes (36 Gy) with VIT, 12 ADJ cycles	SD	CR	N	Nausea, vomiting, diarrhea, constipation, myelosuppression, febrile neutropenia, prolonged GJ tube, malnutrition, abdominal pain, chylous ascites, *C. difficile* infection, partial SBO requiring lysis of adhesions, enterocutaneous fistula	NED	46.7
3	ARST08P1 (VIT, VDC, IE) with 5 NAJ cycles, surgical resection (<2% necrosis, R1), concurrent WART (24 Gyof planned 30 Gy) with VDC/IE, 9 ADJ cycles, transitioned to 6 cycles of pazopanib	PR	CR	N	Nausea, vomiting, diarrhea, constipation, myelosuppression, SOS s/p defibrotide and peritoneal drain, *C. difficile* infection	NED	20.7
4	ARST08P1 (VIT, VDC, IE) with 5 NAJ cycles, surgical resection (0% necrosis, R1, concurrent WART, including cardiophrenic nodule (19.5 Gy) and pelvic boost RT (21.9 Gy, total dose of 41.4 Gy) with VIT, 15 ADJ cycles	PR	CR	N	Nausea, vomiting, diarrhea, constipation, myelosuppression, diarrhea during RT	NED	60.3
5	ARST08P1 (VIT, VDC, IE) with 8 NAJ cycles, surgical resection (30% necrosis, R0), concurrent WART (30 Gy) and pelvic boost RT (14.4 Gy, total dose of 44.4 Gy) with VIT/IE, 7 ADJ cycles (ongoing treatment)	SD	N/A	N/A	Nausea, vomiting, diarrhea, constipation, myelosuppression, mucositis, weight loss, febrile neutropenia	On therapy	10.1
6	ARST08P1 (VIT, VDC, IE) with 5 NAJ cycles, surgical resection (5% necrosis in primary tumor, 100% necrosis, R0) in lymph node, plan for RT to primary, inguinal node and pelvis (55.8 Gy) with concurrent chemotherapy, 2 ADJ cycle (ongoing treatment)	SD	N/A	N/A	Nausea, vomiting, diarrhea, constipation, myelosuppression	On therapy	4.4

Abbreviations: ADJ, adjuvant; CR, complete response; DOD, died of disease; GJ, gastrostomy-jejunostomy; HIPEC, Hyperthermic intraperitoneal chemotherapy; IE, ifosfamide/etoposide; N, no; N/A, not applicable; NAJ, neoadjuvant; NED, no evidence of disease; PD, progressive disease; PR, partial response; R0, resection with no cancer cells seen microscopically at the resection margins of the primary tumor bed; R1, resection with cancer cells present microscopically at the margins of the primary tumor bed; RD, recurrent disease; RT, radiotherapy; SBO, small bowel obstruction; SD, stable disease; SOS, sinusoidal obstruction syndrome; VDC, vincristine/doxorubicin/cyclophosphamide; VIT, vincristine/irinotecan/temozolomide; WART, whole abdomen radiotherapy; WD, with disease; Y, yes