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First-line Anti-GD2 Therapy Combined With Consolidation Chemotherapy in 3 Patients With Newly Diagnosed Metastatic Ewing Sarcoma or Ewing-like Sarcoma

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Summary: Despite multimodal therapy, the prognosis of patients with metastatic Ewing sarcoma (ES) remains poor, with new treatments urgently needed. The disialoganglioside GD2, a well-established tumor-associated antigen, is expressed in 40% to 90% of ES cells, making it a suitable therapeutic target. Here we report 3 cases with newly diagnosed, metastatic, GD2-positive ES or Ewing-like sarcoma treated with the anti-GD2 antibody dinutuximab beta in addition to standard chemotherapeutic regimens. Treatment was well-tolerated, and all patients achieved complete remission, without evidence of relapse. First-line anti-GD2 immunotherapy in patients with metastatic, GD2-positive ES or Ewing-like sarcoma represents a promising therapeutic option that warrants further clinical evaluation.

Key Words: Ewing sarcoma, immunotherapy, anti-GD2 therapy, dinutuximab beta, case report

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Ewing sarcoma (ES) is a cancer of mesenchymal origin, primarily affecting bone and surrounding tissues, and is most commonly seen in children and young adults.[1,2] Approximately 25% of patients are diagnosed with metastatic disease, with lung, bone and bone marrow being the most common sites of metastasis.[3] The current standard of care for ES is multimodal, utilizing combination chemotherapies, radiotherapy and surgery,[1] with successful management of localized disease associated with survival rates of 70% to 80%.[2] In Europe, patients with ES are generally treated with VIDE (vincristine [V], doxorubicin [D], cyclophosphamide [C]/ifosfamide [I], etoposide [E]) induction chemotherapy, followed by local therapy, such as surgery or radiation therapy, and VAI or VAC (V, actinomycin-D, I or cyclophosphamide [C]) consolidation therapy.[3] In a recent study in patients with ES from 10 different European countries, the US regimen of compressed VDC/IE induction and IE/VC consolidation was found to be superior to the European regimen for both event-free survival and overall survival, with no excess toxicity.[4] While patients with metastatic disease are generally treated with the same approach as patients with localized disease, the prognosis is much worse, with a survival probability of ~20% to 40%, dependent on metastatic sites and tumor burden.[2,3,5] High treatment-related morbidity due to the use of aggressive front-line therapeutic regimens are additional factors that contribute to poor outcomes in these patients.[2] In recent years, there have been advances in the diagnostic and molecular characterization of ES, but despite this, new targeted agents are needed to further improve patient outcomes and survival, especially in patients with metastatic disease.[2,6]

The disialoganglioside GD2, a glycosphingolipid involved in cell proliferation, is an established tumor-associated antigen present on multiple tumor types, including neuroblastoma, but has limited expression in normal tissues.[6–9] Expression of GD2 is also highly prevalent in other pediatric solid tumors, such as ES and osteosarcoma.[9] In ES, GD2 is expressed throughout various disease manifestations, including localized, disseminated or relapsed disease,[10] with expression levels ranging from 40% to 90% in biopsy samples, making it a potentially useful therapeutic target in this malignancy.[2,9]

Anti-GD2 antibodies such as dinutuximab and dinutuximab beta bind to GD2 on tumor cells targeting these cells for destruction by the body's own immune system.[7,9] Studies by the Children's Oncology Group (COG) have shown that immunotherapy with dinutuximab, interleukin-2 and granulocyte-macrophage colony-stimulating factor can improve outcomes in patients with high-risk neuroblastoma when given as maintenance therapy following induction and consolidation therapy, which led to the approval of this antibody in the United States.[11–13] Similarly, dinutuximab beta was approved for use in neuroblastoma in Europe, based on the positive results of the SIOPEN (International Society for Paediatric Oncology European Neuroblastoma) studies.[14–17] The addition of an anti-GD2 antibody, such as

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dinutuximab beta, to an existing cytotoxic regimen also has the potential to increase survival and reduce progression in other tumors with high GD2 expression levels.[9] There are currently several ongoing clinical trials investigating anti-GD2 approaches in osteosarcoma,[9] and the combination of dinutuximab beta and chemotherapy has also demonstrated clinical activity in an individual case with refractory ES, warranting further investigation.[8,18]

In this report, we describe the disease characteristics and clinical outcomes of 2 patients with newly diagnosed, metastatic, GD2-positive ES and 1 patient with newly diagnosed, metastatic, GD2-positive Ewing-like sarcoma (ELS) treated with dinutuximab beta in addition to cytotoxic chemotherapy regimens.

MATERIALS AND METHODS

Two patients with metastatic ES and 1 with metastatic ELS attended the Department of Pediatrics and Medical Genetics, Division of Pediatric Oncohematology, Plovdiv, Bulgaria. All patients received the EWING 2012 protocol, which consists of 6 cycles of VIDE (V, 1.5 mg/m^2; I, 3000 mg/m^2; D, 20 mg/m^2; E, 150 mg/m^2) induction chemotherapy, each cycle lasting 21 days, followed by 8 cycles of VAI (V, 1.5 mg/m^2; A, 0.75 mg/m^2; I, 3000 mg/m^2) consolidation chemotherapy, each cycle lasting 21 days. After the first VAI cycle, the patients received 1 cycle of dinutuximab beta (10 mg/m^2/d over 10 d), followed by surgery and irradiation of the primary tumor (54 Gy). The remaining 4 cycles of dinutuximab beta were given after VAI cycles 3, 5 and 7, and 21 days after completion of the final VAI cycle, with radiation and surgery of metastases performed after VAI cycle 4. Dinutuximab beta, which is not currently approved for the treatment of ES, was administered under compassionate use as a long-term infusion, in line with the recent SIOPEN recommendation for the treatment of neuroblastoma.[16] The use of dinutuximab beta was approved by the Executive National Drug Agency and a steering committee of 3 Pediatric Oncohematologists. An overview of the treatment schedule is shown in Figure 1A. Granulocyte colony-stimulating factor was given alongside dinutuximab beta but was discontinued if granulocytes reached $>500/\mu L$. As supportive therapy, the patients received gabapentin, intravenous tramadol, and paracetamol/metamizole if needed.

GD2 and CD99 expression were assessed using immunohistochemistry in paraffin-embedded tumor specimens. For GD2 detection, slides of paraffin-embedded tumor specimens were subjected to a fully automated immunohistochemistry staining using the BenchMark ULTRA device (Roche). The primary antibody, murine anti-GD2 antibody 14G2a (IgG2a), was used at a final concentration of 0.3 to 0.6 μg/mL, and incubated for 32 minutes at 37°C. For visualization, the ultraView Universal DAB Detection Kit (Ventana), specifically developed for the sensitive detection of mouse and rabbit primary antibodies, was used according to the manufacturer's guidelines. CD99 expression was detected using the primary antibody FLEX monoclonal murine anti-CD99 (*MIC2* gene product, clone 12E7, isotype IgG1 kappa, DAKO) with DAKO Autostainer/Autostainer Plus instruments, according to the manufacturer's guidelines.

Additional tumor makers were assessed using immunohistochemistry (ie, S100, CD56, Ki67, synaptophysin, chromogranin, desmin, myogenin neuron-specific enolase and thyroid transcription factor) and fluorescence in situ hybridization (ie, EWS-FLI1, EWSR1, and CIC-DUX4). Treatment response was evaluated locally using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Other study assessments included computed tomography (CT), positron emission tomography, magnetic resonance imaging (MRI), and trephine biopsy followed by flow cytometry. Patients were also monitored for adverse events, which were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

RESULTS

Patient and disease characteristics are presented in Table 1. Histological analysis of biopsy tissue from all 3 primary tumors revealed CD99 expression (Fig. 1B). GD2 expression was also confirmed in all 3 tumor specimens before the start of dinutuximab beta treatment (Fig. 1C). The new treatment regimen was well-tolerated by all patients, with no severe side effects reported. All patients reported slight to moderate pain and mild hypoproteinemia during the first cycle (all grade 1/2), in line with the known safety profile of dinutuximab beta in neuroblastoma. One patient experienced a febrile episode (grade 1/2) due to a urinary tract infection which was likely related to chemotherapy and resolved upon treatment with antibiotics. The side effects (all grade 1/2) associated with VAI cycles did not appear to be augmented by adding dinutuximab beta to the chemotherapy backbone. All 3 patients achieved complete remission, without evidence of relapse. As of March 2022, all patients had completed therapy, and complete response is still ongoing, with a duration ranging from 14 to 19 months (Fig. 2A).

Patient 1

A 3-year-old with torticollis, supraclavicular tumor mass and brachial plexus palsy was admitted in April 2020. The initial MRI showed a cervical paraspinal tumor mass with local spinal cord compression (Fig. 2B, left panel in top row), and a chest CT revealed a single pulmonary metastasis. Because the imaging results and the age of the patient were suspicious of neuroblastoma, the patient was started on chemotherapy with 3 cycles (cycle A, B, and C) of Rapid COJEC (cisplatin [C], vincristine [O], carboplatin [J], etoposide [E], and cyclophosphamide [C]), an induction chemotherapy usually offered to patients with high-risk neuroblastoma, which achieved an excellent response with spinal cord decompression on the following day. A biopsy of the cervical mass was performed after the first COJEC cycle, and paraspinal ES was proven after a second pathomorphological revision. The lung metastasis was also histologically confirmed after total resection (with poor surgical margins of 0.1 mm/R2).

The patient was switched to chemotherapy using the EWING 2012 protocol plus local radiotherapy of the primary tumor of 40 Gy. MRI following VIDE induction therapy and before dinutuximab beta treatment demonstrated partial response of the primary tumor (Fig. 2B, central panel in top row), and the lung metastasis was no longer evident. Total surgical removal of the residual primary tumor (R1) was performed after the first cycle of VAI and dinutuximab beta, with histology revealing complete tumor necrosis. After the surgery, the patient received the remaining VAI and dinutuximab beta cycles. MRI following treatment completion demonstrated no evidence of residual primary tumor (Fig. 2B, right panel in top row).

Patient 2

A 16-year-old who presented with sudden pain in the thoracic region of the spinal cord followed by paralysis of both legs was diagnosed with metastatic ES in March 2020. Initial CT

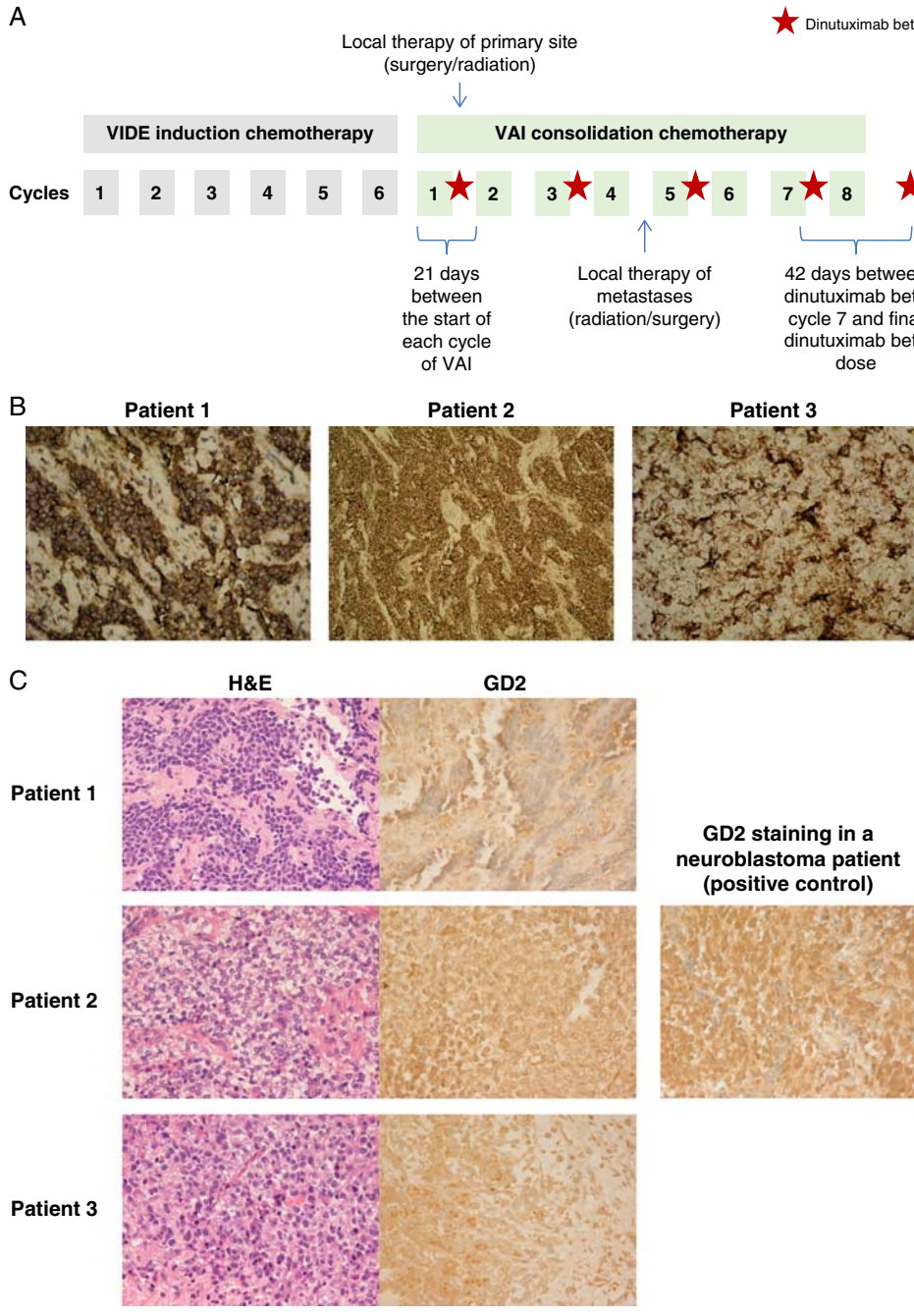

FIGURE 1. A, Overview of the treatment schedule. Induction chemotherapy dosing: vincristine 1.5 mg/m^2, ifosfamide 3000 mg/m^2, doxorubicine 20 mg/m^2, etoposide 150 mg/m^2, actinomycin-D 0.75 mg/m^2 (VIDE). Consolidation chemotherapy dosing: vincristine 1.5 mg/m^2, actinomycin-D 0.75 mg/m^2, ifosfamide 3000 mg/m^2 (VAI). Dinutuximab beta was started on the first day after the completion of the VAI cycles 1, 3, 5, and 7, and 21 days after completion of VAI cycle 8. Granulocyte colony-stimulating factor was given simultaneously with dinutuximab beta, and was discontinued when granulocytes were $>500/\mu L$. B, CD99 expression in paraffin-embedded tumor specimens from all 3 patients. C, GD2 expression in paraffin-embedded tumor specimens of the 3 patients with ES and a patient with neuroblastoma (included as positive control). Tumor cells were confirmed by H&E staining (left panels) and GD2 expression was shown by immunohistochemistry using murine anti-GD2 antibody 14G2a (right panels; brown). GD2 indicates disialoganglioside 2; H&E, hematoxylin and eosin; VAI, vincristine, actinomycin-D, ifosfamide; VIDE, vincristine, ifosfamide, doxorubicine, etoposide.

and MRI located a thoracic spinal tumor with total spinal compression (Fig. 2B, left panel in middle row) and a single metastasis in the lung. No bone marrow involvement or distant bone metastases were observed. The spinal cord was surgically decompressed and subtotal resection of primary tumor and pulmonary metastasis (R2) was performed. Histological analysis of resected tissue from the primary tumor and the lung metastasis confirmed the diagnosis of metastatic ES.

TABLE 1. Patient and Disease Characteristics

	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Female
Age at diagnosis (y)	3	16	13
Stage at diagnosis	AJCC IVA (T1N0M1aG3)	AJCC IVA (T1N0M1aG3)	AJCC IVA (T2N0M1aG3)
Ewing sarcoma characteristics	Positive CD99 GD2	Positive CD99, S100, EWS-FLI1 GD2	Positive CD99, CIC-DUX4 fusion GD2
	Negative S100, CD56, NSE, synaptophysin, TTF, chromogranin, desmin	Negative NSE, synaptophysin, chromogranin	Negative EWSR1, myogenin, desmin
	Ki67 high-proliferative activity in >50% of the cells	Ki67 high-proliferative activity in ~97% of the cells	Ki67 high-proliferative activity in ~40% of the cells
Clinical picture	Torticollis, supraclavicular tumor mass and brachial plexus palsy on the right side. Local spinal cord compression	Pain in the thoracic region of the spinal cord and paralysis of both legs. No fever or weight loss recorded	Painless, firm tumor mass 21×14 cm in size, distorting the distal part of the left thigh. Pain on knee flexion and displacement of the patella. No fever or weight loss reported
Primary tumor	Paraspinal tumor (31/34/23 mm)	Thoracic spine: Th 6-8 (extraspinal: 37/18/25 mm and intraspinal: 54/11 mm component). Involvement of the paravertebral muscles	Left femur (coronal plane: 21/14 cm; sagittal plane: 20/8 cm)
Metastases	Lung (single metastasis in the left lung, 6 mm in size)	Lung (single metastasis in the right lung, 36 mm in size)	Lung (multiple bilateral metastases: 3 right lung metastases >5 mm (7, 8, 10 mm) and 10 micronodules <5 mm; 1 left lung metastasis (8 mm) and 5 micronodules <5 mm

AJCC indicates American Joint Committee on Cancer; CD99, cluster of differentiation 99; CD56, cluster of differentiation 56; CIC-DUX4, Capicua-double homeobox 4; EWS-FLI1, Ewing sarcoma breakpoint region 1, friend leukemia integration 1 transcription factor; EWSR1, EWS RNA binding protein 1; GD2, disialoganglioside 2; NSE, neuron-specific enolase; TTF, thyroid transcription factor.

The patient was started on VIDE chemotherapy and at the end of the induction phase, no residual tumor mass was detected in the thoracic spine on MRI (Fig. 2B, central panel in middle row) and no lung metastases were observed on CT scan. Therapy was continued with VAI, dinutuximab beta, local irradiation of the thoracic spine and whole lung irradiation. MRI following treatment completion confirmed the absence of a residual tumor mass in the thoracic spine and the lung (Fig. 2B, right panel in middle row).

Patient 3

A 13-year-old with a painless, solid tumor mass in the left thigh was diagnosed with metastatic ELS in June 2020. While histological analysis of a biopsy sample demonstrated that the tumor was CIC-DUX4-positive (Table 1), an initial MRI demonstrated a tumor mass encompassing the ventral, medial and lateral part of the left femur near the lateral condyle (Fig. 2B, left panel in bottom row), resembling classical bone ES. High-resolution chest CT detected multiple pulmonary metastases but no enlarged lymph nodes. Trephine biopsy demonstrated no evidence of bone marrow infiltration.

Based on the MRI finding, the patient received therapy for ES, starting with VIDE induction therapy. After the first cycle, positron emission tomography CT showed that the primary tumor was metabolically active but reduced in size. Pulmonary metastases were also reduced in size after the first cycle and nearly completely regressed after the third cycle of VIDE. MRI after completion of VIDE therapy revealed a substantial reduction of the primary tumor (Fig. 2B, central panel in bottom row). The patient went on to receive consolidation therapy. After the first cycle of VAI and dinutuximab beta, MRI demonstrated further reduction of the primary tumor (Fig. 2B, right panel in bottom row) and high-resolution chest CT revealed total regression of the pulmonary metastases. The residual primary tumor was removed during subsequent limb-sparing surgery (R0), with histology of the resected tumor tissue demonstrating 100% tumor necrosis. Despite the regression of the metastases, whole lung irradiation was performed. The patient continued to receive the remaining cycles of consolidation therapy with VAI and dinutuximab beta. CT following treatment completion revealed no evidence of residual primary tumor.

DISCUSSION

The new treatment approach combining dinutuximab beta with a cytotoxic chemotherapy regimen was well-tolerated in all 3 patients with metastatic, GD2-positive ES or ELS, with no severe side effects reported. All patients achieved complete remission of the primary tumor and metastases, with an ongoing duration of response ranging from 14 to 19 months as of March 2022. One of the patients had no primary tumor after VIDE therapy, while the other 2 patients exhibited remaining primary tumors after induction, both of which demonstrated complete necrosis following 1 cycle of VAI and dinutuximab beta.

Targeting GD2 with dinutuximab beta is the standard of care approach to treating high-risk neuroblastoma in the maintenance setting in Europe and has significantly improved survival for patients with this malignancy.[9,16,19] Evidence

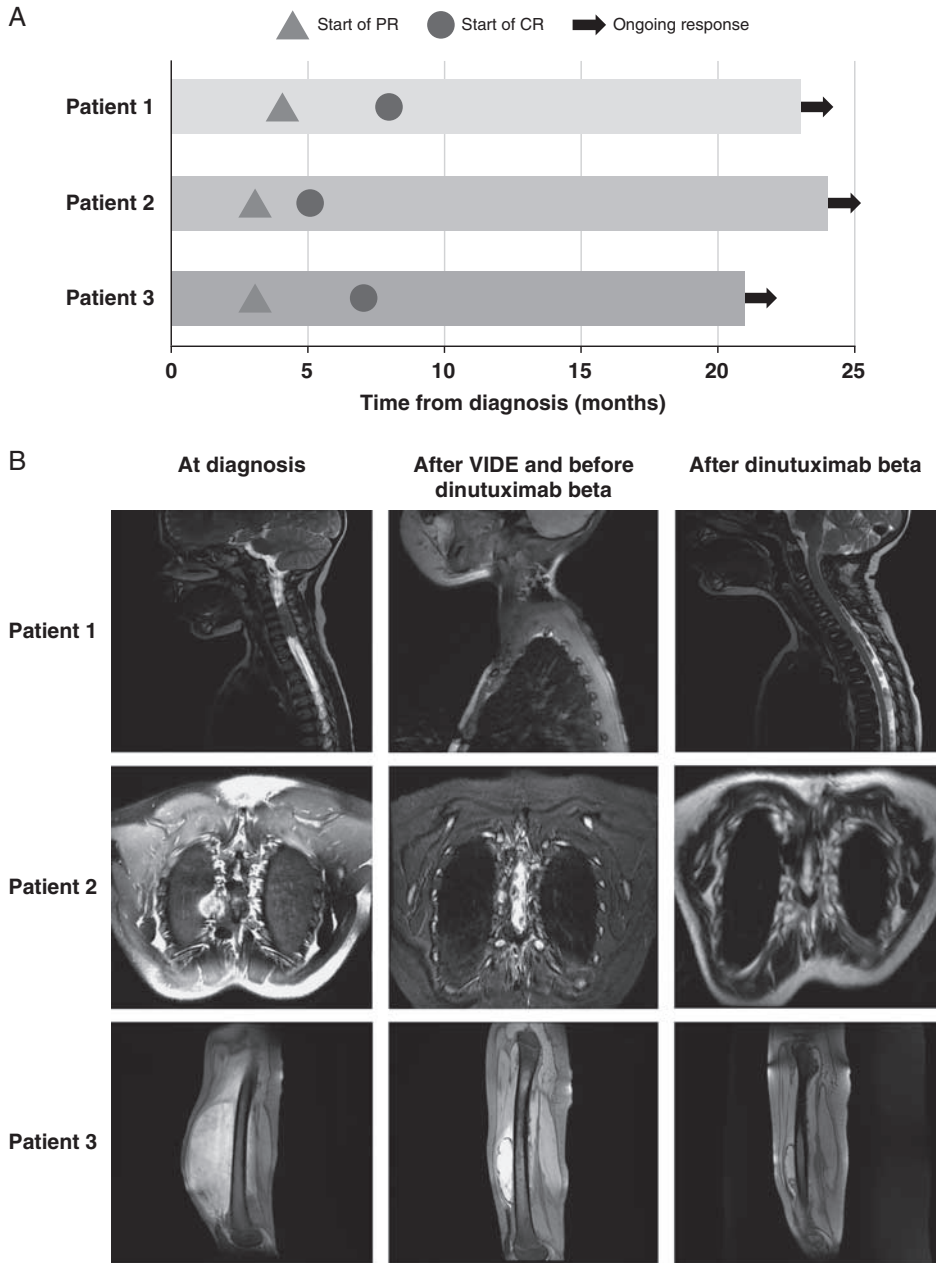

FIGURE 2. A, Duration of response from diagnosis. PR occurred within 3 to 4 months of diagnosis and CR after another 2 to 4 months. Responses are still ongoing as of March 2022. B, MRI scans of the primary tumor for patient 1 (top row), patient 2 (middle row) and patient 3 (bottom row) at diagnosis (left panels), after VIDE therapy and before dinutuximab beta (central panels) and after dinutuximab beta (right panels). Please note that the MRI in the right panel for patient 3 was performed after the first cycle of dinutuximab beta but before surgery. CR indicates complete response; MRI, magnetic resonance imaging; PR, partial response; VIDE, vincristine, ifosfamide, doxorubicine, etoposide.

suggests that early use of anti-GD2 immunotherapy—during or after induction chemotherapy and before surgery—may also be beneficial in patients with high-risk neuroblastoma,[20–23] including those with relapsed/refractory disease.[24,25] The FDA-approved anti-GD2 antibody dinutuximab demonstrated significant anti-tumor activity in children with refractory or relapsed neuroblastoma when used in combination with chemotherapy,[24,25] and pediatric dosing strategies, schedules and toxicities are well-documented with this therapy combination.[18] Clinical trials investigating dinutuximab beta in combination with chemotherapy in patients with relapsed/refractory neuroblastoma are currently ongoing.

High GD2 expression levels in ES and ELS indicate that these tumors could also be successfully targeted with GD2-directed therapy, and in a recent case report, dinutuximab beta given alongside chemotherapy has demonstrated clinical activity in a patient with refractory ES.[8] Our findings provide further evidence that anti-GD2 immunotherapy added to chemotherapy might be a suitable treatment option for patients with metastatic ES or ELS.

While dinutuximab beta is approved for use as maintenance therapy in neuroblastoma,[17] it is not currently indicated for the treatment of ES or ELS. However, based on the promising results reported with the use of early immunotherapy and a combination of immunotherapy and chemotherapy in neuroblastoma,[20–25] we treated our patients with GD2-positive ES and ELS in a similar way. We combined dinutuximab beta treatment with consolidation therapy, with 1 cycle of dinutuximab beta being administered before surgery and the remaining cycles during the postoperative phase, in between VAI cycles. Administering the remaining cycles during rather than postconsolidation ensures that the period without immunotherapy is minimized, which may avoid possible drug resistance.

While our case report has several limitations, including the small patient number, the short follow-up duration and its retrospective nature, our findings, in addition to previous results achieved with anti-GD2 therapy in neuroblastoma, suggest that a treatment approach combining anti-GD2 immunotherapy and chemotherapy might be worth exploring in a wider clinical study in patients with ES and/or ELS, especially those with metastatic disease.

The high expression of GD2 in some ES/ELS biopsies may be an important factor to aid in treatment selection and the journey toward a personalized medicine approach for these patients.[8] We were able to confirm GD2 expression in the biopsies from our patients before dinutuximab beta treatment. However, identification of GD2 on cells using immunohistochemistry has been inconsistent, and a standardized approach to detecting this marker is needed to be able to routinely categorize tumors based on GD2 expression.[18]

Overall, our findings suggest that anti-GD2 immunotherapy combined with chemotherapy in patients with newly diagnosed, metastatic ES or ELS represents a promising therapeutic option that warrants further clinical evaluation.

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