Extended cycles of anti-GD2 antibody dinutuximab beta treatment combined with chemotherapy in patients with relapsed or refractory neuroblastoma: A retrospective study

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Abstract. Relapsed or refractory high-risk neuroblastoma (R/R HR-NB) is associated with a poor prognosis. Although 5 cycles of anti-GD2 immunotherapy with dinutuximab beta show efficacy, the regimen needs optimization. The present study evaluated the use of extended dinutuximab beta immunotherapy combined with chemotherapy in pediatric patients with R/R NB. In this single-center retrospective study, children with a median age 5.1 years (range, 2.0-11.1 years) with R/R HR-NB who were treated with >5 cycles of dinutuximab beta (10 mg/m^2/day for 10-days per 35-day cycle), granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin, plus chemotherapy, were included. The primary outcome of the study was objective response rate (ORR). Secondary outcomes included disease control rate, progression-free survival (PFS), overall survival (OS) and safety. A total of 30 patients (24 refractory and 6 relapsed) received dinutuximab beta immunotherapy for a median of 7 cycles (range, 6-12 cycles). Patients with residual disease showed the best ORR of 65%. ORR and complete response (CR) rates improved from 40 and 20%, respectively, at cycle 5/6, to 55 and 30%, respectively, with extended therapy. Notably, 38.5% of patients achieved the best response during cycles beyond the standard 5 cycles. The CR maintenance rate was 90% of patients without residual disease. The 2-year PFS and OS rate were 83.2 and 94.7%, respectively, with higher outcomes in CR patients (2-year PFS rate, 90.0%; 2-year OS rate, 100.0%). Commonly observed grade ≥3 adverse events during the extended phase included infections (90%), neutropenia (86.7%), leukopenia (63.3%) and pain (53.3%), and were generally manageable. No immune-related deaths occurred. Overall, cycles beyond the standard 5 cycles of dinutuximab beta with chemoimmunotherapy were effective and tolerable in pediatric patients with R/R HR-NB, demonstrating improved response and survival outcomes.

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Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children, accounting for 8-10% of all pediatric cancers and 15% of cancer-related deaths worldwide (1,2). According to the Global Burden of Disease 2021 report, the incidence rate increased from 0.25 cases per 100,000 individuals in 1990 to 0.28 cases per 100,000 individuals in 2021, representing an overall increase of 12% (3). NB, which originates from neural crest cells of the sympathetic nervous system, is a biologically and clinically heterogeneous tumor. High-risk NB (HR-NB), which constitutes ~50% of new diagnoses, typically presents with metastases (e.g. bone marrow [BM], bone and lymph node metastases), MYCN proto-oncogene bHLH transcription factor (MYCN) amplification or unfavorable histological features. These factors are strongly associated with a poor prognosis, with a 5-year overall survival (OS) rate of <50% (4,5). Despite intensive therapy, relapsed or refractory (R/R) disease remains the primary cause of treatment failure, and ~60% of HR patients experience disease recurrence. The survival rate following relapse is <20%, highlighting the urgent need for novel and more effective therapeutic strategies (6).

Immunotherapy, particularly targeting disialoganglioside GD2, which is highly expressed on NB cells, has emerged as a promising option for R/R NB. Dinutuximab beta, a monoclonal GD2-targeting antibody, was approved in China in August 2021 for treating patients with HR-NB who were ≥12 months old, including R/R patients (7). The National Comprehensive Cancer Network guidelines recommend the use of anti-GD2 immunotherapy in combination with chemotherapy to enhance tumor remission and survival in patients with R/R NB (8). An increasing number of studies have also provided empirical medical evidence for the treatment strategy of chemoimmunotherapy. The BEACON-Immuno

phase II trial showed that dinutuximab beta plus temozolomide/topotecan improved overall response rate (ORR) by 17% and 1-year progression-free survival (PFS) rate from 27 to 57% compared with chemotherapy alone (9). Two other studies have also provided supportive evidence for the efficacy of chemoimmunotherapy in R/R NB. A phase II Children's Oncology Group study demonstrated that dinutuximab combined with irinotecan, temozolomide and granulocyte-macrophage colony-stimulating factor (GM-CSF) was tolerable and resulted in clinically meaningful responses in heavily pretreated patients (10), while a recent meta-analysis reported that GD2-targeting monoclonal antibody therapy combined with chemotherapy significantly improved tumor remission rates, event-free survival and OS in this population (11). A retrospective study of dinutuximab beta combined with chemotherapy in R/R NB showed 64% of ORR, with 32% achieving complete response (CR). Notably, 31% of responders achieved a CR or partial response (PR) after 6 to 8 cycles, with some benefiting from up to 10 cycles of treatment, suggesting that extended immunotherapy may improve outcomes (12).

Further studies are needed to optimize the duration of immunotherapy and enhance its efficacy in this difficult-to-treat population. The present retrospective study assessed the efficacy and safety of extended treatment cycles of dinutuximab beta and chemotherapy in patients with R/R NB who had undergone >5 cycles of dinutuximab beta immunotherapy.

Materials and methods

Study design and patients. The present study was a single-center, retrospective study that included patients with R/R NB who were treated in the Department of Pediatric Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (Jinan, China), between January 2022 and October 2024. Eligible patients were classified as HR according to the International Neuroblastoma Risk Group (INRG) Staging System (13), and were ≥12 months old at the initiation of dinutuximab beta treatment. Patients with R/R NB who received >5 cycles of dinutuximab beta were included in the study. Refractory NB was defined as either the patient that failed to achieve a PR or CR after induction chemotherapy or one in which the residual lesion was confirmed as active disease following induction and consolidation therapy [as assessed by ^{18}F-NOTATATE positron emission tomography/computed tomography (PET/CT), iodine-123 or iodine-131 meta-iodobenzylguanidine scintigraphy, or biopsy]. Relapsed NB was defined as the patient that achieved a CR after previous intensive multimodal treatment for 4 weeks, followed by the emergence of new active lesions. Patients with concurrent malignancies other than NB or those who had not ended dinutuximab beta immunotherapy were excluded. The study was approved by the Ethics Committee of Shandong First Medical University and Shandong Academy of Medical Sciences (approval no. SDTHEC202503192).

Treatment regimen. The treatment regimen included dinutuximab beta combined with chemotherapy, GM-CSF and isotretinoin. Dinutuximab beta was administered through central venous access as a continuous long-term infusion at a dose of 10 mg/m^2/day from days 1 to 10 of each 35-day cycle. GM-CSF was administered at a dose of 250 μg/m^2/day from days 6 to 12. GM-CSF was discontinued if the absolute neutrophil count was >20x10^9/l. Isotretinoin was orally administered at a dose of 160 mg/m^2/day, in two divided doses from days 15 to 28. Chemotherapy was also administered, and the regimens were mainly temozolomide-based, including 1.5 mg/m^2 vincristine on day 1, 50 mg/m^2 irinotecan on days 1 to 5, 100 mg/m^2 temozolomide on days 1 to 5 (vincristine-irinotecan-temozolomide [VIT] regimen), or platinum-based chemotherapy. The latter included the DE regimen, consisting of cisplatin at 20 mg/m^2 and etoposide at 100 mg/m^2, both administered on days 1 to 4, the OPET regimen, consisting of vincristine at 1.5 mg/m^2 on day 1, cisplatin at 25 mg/m^2, etoposide at 100 mg/m^2 and temozolomide at 100 mg/m^2, each administered on days 1 to 3, and the OPEC regimen, consisting of vincristine at 1.5 mg/m^2 on day 1, cisplatin at 25 mg/m^2, etoposide at 100 mg/m^2 and cyclophosphamide at 400 mg/m^2, each administered on days 1 to 3. The treatment regimen is illustrated in Fig. 1.

Regarding dinutuximab beta immunotherapy, if a CR was achieved after 5 cycles, an additional 2 to 4 cycles could be administered based on the clinical evaluation and patients conditions, to maintain CR and eradicate minimal residual disease. If a CR was not achieved, in consideration of the absence of other treatment measures with greater advantages, it was recommended to extend the immunotherapy cycles of dinutuximab beta and evaluate once every 2 or 3 cycles until the best response was achieved, or until disease progression or intolerable toxicity.

Assessment and outcomes. The overall tumor response was assessed using the revised International Neuroblastoma Response Criteria (14). BM involvement was detected by the presence of tumor cells in the BM by immunocytology and immunohistochemistry. Bone and soft tissues were evaluated using ^{18}F-NOTATATE-PET/CT imaging. Owing to the unavailability of ^{68}Ga, the ^{18}F-NOTATATE-PET/CT imaging technique is adopted for tumor assessment in Shandong Cancer Hospital and Institute. The imaging mechanism is comparable with that of ^{68}Ga-DOTATATE-PET/CT (15,16), as both involve the imaging of octreotide derivatives.

The primary outcome was the best ORR (most favorable response achieved by a patient at any time during the treatment period, calculated as the proportion of patients with best response) during the immunotherapy period. The secondary outcomes were ORR [proportion of patients achieving a tumor response (CR or PR)], disease-control-rate (DCR), PFS, OS and safety. The best response was defined as the most favorable tumor response observed from the initiation of immunotherapy to the end of therapy. PFS time was defined as the time from the initiation of dinutuximab beta to disease progression or death from any cause, or until the last contact with the patient. OS time was defined as the time from the initiation of dinutuximab beta to death from any cause, or until the last contact with the patient.

Patients were monitored for adverse events (AEs) following the Common Terminology Criteria for Adverse Events Version 5.0 (17), Grade ≥3 treatment-related AEs (TRAEs) were reported.

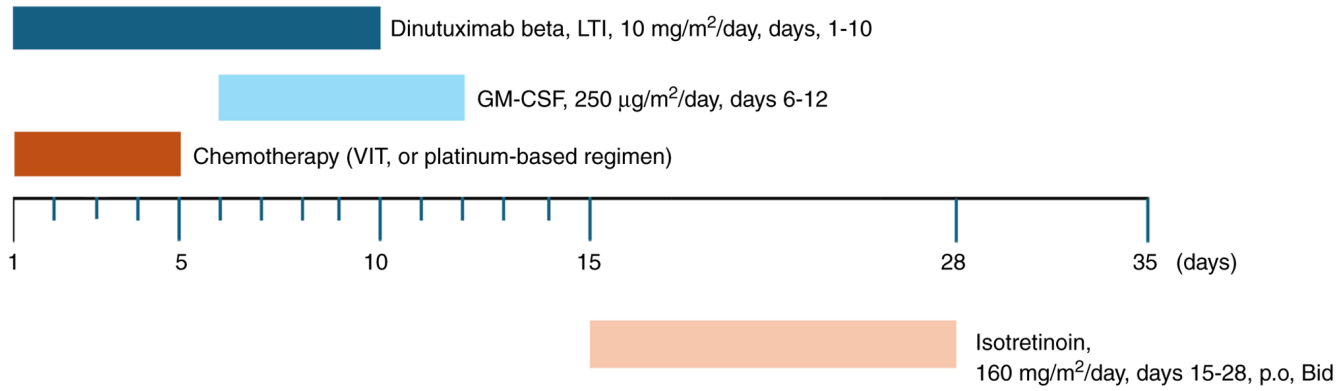

Figure 1. Treatment regimens and dosing schedules of chemoimmunotherapy used in relapsed or refractory neuroblastoma. The VIT regimen consisted of 1.5 mg/m^2 vincristine on day 1, 50 mg/m^2 irinotecan on days 1-5 and 100 mg/m^2 temozolomide on days 1-5. The platinum-based regimens included DE (20 mg/m^2 cisplatin on days 1-4 and 100 mg/m^2 etoposide on days 1-4), OPET (1.5 mg/m^2 vincristine on day 1, 25 mg/m^2 cisplatin on days 1-3, 100 mg/m^2 etoposide on days 1-3 and 100 mg/m^2 temozolomide on days 1-3) or OPEC (1.5 mg/m^2 vincristine on day 1, 25 mg/m^2 cisplatin on days 1-3, 100 mg/m^2 etoposide on days 1-3 and 400 mg/m^2 cyclophosphamide on days 1-3). LTI, long-term infusion; GM-CSF, granulocyte-macrophage colony-stimulating factor; p.o., oral; Bid, twice a day.

Statistical analysis. Patients with residual disease prior to immunotherapy were included in the ORR and DCR analyses, assuming a binomial distribution with 95% confidence intervals (CIs). PFS and OS were estimated using the Kaplan-Meier method, with comparisons via log-rank test. The 2-year PFS and OS rates were reported with 95% CIs. Stratified analysis assessed PFS and OS based on pre-immunotherapy disease status (CR vs. non-CR). Cox proportional hazards regression analysis was performed to assess the prognostic impact of clinical outcomes. Median follow-up was estimated using the inverse Kaplan-Meier method. All analyses were conducted using SPSS v22.0 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. A total of 30 patients were included, with a median age at diagnosis of 3.9 years (range, 0.6-9.7 years), and a median age at the initiation of dinutuximab beta treatment of 5.1 years (range, 2.0-11.1 years). Among them, 24 patients (80%) had refractory NB and 6 patients (20%) had relapsed NB. Furthermore, 3 patients (10%) had MYCN amplification, 13 patients (43.3%) had 11q deletion and 3 patients (10%) had 1p deletion. All patients were diagnosed as stage 4 according to the International Neuroblastoma Staging System, and stage M according to the INRG Staging System. A total of 28 patients (93.3%) were observed with a primary tumor in the abdomen. The baseline characteristics are presented in Table I.

Prior to dinutuximab beta treatment, 10 patients (33.3%) had no residual disease and achieved a CR, 2 patients (6.7%) achieved a PR, 14 patients (46.7%) achieved a minor response and 4 patients (13.3%) experienced progressive disease (PD). Among the 20 patients with residual disease, 12 (60%) had bone metastases solely, 4 (20%) had both bone and soft tissue metastases, 2 (10%) had bone and BM metastases, 1 patient (5%) had BM metastasis solely, and 1 patient (5%) had bone, soft tissue and BM metastases together. Additionally, 23 of the total patients (76.7%) had undergone stem cell transplantation, and 28 patients (93.3%) had undergone radiation therapy. All patients had received chemotherapy in their previous treatment, and the median number of cycles of previous chemotherapy was 10. All patients received dinutuximab beta immunotherapy, which was combined with chemotherapy; 26 patients (86.7%) received a temozolomide-based chemotherapy regimen, whereas 13 patients (43.3%) received a platinum-based chemotherapy regimen (12 patients received both regimens). All patients received immunotherapy, with the median number of cycles of dinutuximab beta treatment being 7 cycles, ranging from 6 to 12 cycles. The median follow-up time was 18 months (range, 9-35 months). The details related to clinical treatment are presented in Table II.

Efficacy

Tumor response. The response rates were evaluated in the 20 patients with residual disease prior to immunotherapy. During the immunotherapy period, the best ORR was observed to be 65% (95% CI, 40.8-84.6%), including 6 instances of a CR and 7 of a PR. The best DCR was observed to be 100.0%, including 6 instances of a CR, 7 of a PR and 7 of SD. At cycle 3 of dinutuximab beta immunotherapy, the ORR was 25% (95% CI, 8.6-49.1%), DCR was 95% (95% CI, 75.1-99.9%) and the CR rate was 15% (95% CI, 3.2-37.9%), while at cycle 5 or 6, the ORR was 40% (95% CI, 19.1-63.9%), the DCR was 100.0% and the CR rate was 20% (95% CI, 5.7-43.7%). At the end of dinutuximab beta immunotherapy, the ORR was 55% (95% CI, 31.5-76.9%), the DCR was 90% (95% CI, 68.3-98.8%) and the CR rate was 30% (95% CI, 11.9-54.3%). It showed that ORR improved by 15% from 40% at the end of cycle 5 or 6 to 55% at the end of the extended cycles of dinutuximab beta immunotherapy; moreover, the CR rate improved by 10% from 20% at the end of cycle 5 or 6 to 30% at the end of extended immunotherapy. The detailed data are presented in Table III.

Notably, 13 patients showed the best tumor response, 5 patients achieved the best response after >5 cycles of dinutuximab beta treatment, including 2 patients with SD at the end of cycle 5 who improved to CR after cycles beyond the standard 5, and 3 patients who converted from SD to PR, implying 38.5% (5/13 patients) showed improvement from cycles beyond the standard 5 of immunotherapy. Additionally, among the 10 patients without residual disease prior to

Table I. Patient (n=30) and disease characteristics.

Characteristics	Value
Age, years	
Median age at diagnosis (range)	3.9 (0.6-9.7)
Median age at the initiation of dinutuximab beta treatment (range)	5.1 (2.0-11.1)
Sex, n (%)	
Female	13 (43.3)
Male	17 (56.7)
Disease type, n (%)	
Relapsed	6 (20.0)
Refractory	24 (80.0)
MYCN status, n (%)	
Amplified	3 (10.0)
Non-amplified	27 (90.0)
Unknown	0 (0.0)
11q deletion, n (%)	
Yes	13 (43.3)
No	11 (36.7)
Unknown	6 (20.0)
1p deletion, n (%)	
Yes	3 (10.0)
No	21 (70.0)
Unknown	6 (20.0)
INSS stage at diagnosis, n (%)	
Stage 4	30 (100.0)
INRG stage at diagnosis, n (%)	
Stage M	30 (100.0)
Primary tumor localization, n (%)	
Abdomen	28 (93.3)
Chest	1 (3.3)
Neck	0 (0.0)
Other	1 (3.3)

INSS, International Neuroblastoma Staging System; INRG, International Neuroblastoma Risk Group; MYCN, MYCN proto-oncogene bHLH transcription factor.

Table II. Clinical characteristics and disease status of all patients (n=30) prior to immunotherapy.

Characteristics	Value
Status prior to the initiation of dinutuximab beta, n (%)	
CR	10 (33.3)
PR	2 (6.7)
MR	14 (46.7)
PD	4 (13.3)
Metastases site prior to dinutuximab beta treatment, n (%)	
Bone marrow only	1 (3.3)
Bone only	12 (40.0)
Bone and bone marrow	2 (6.6)
Bone and soft tissue	4 (13.3)
Bone and soft tissue and bone marrow	1 (3.3)
Stem cell transplantation, n (%)	
Single transplantation	22 (73.3)
Tandem transplantation	1 (3.3)
No transplantation	7 (23.3)
Radiotherapy, n (%)	
Yes	28 (93.3)
No	2 (6.7)
Cycles of previous chemotherapy, n (%)	
8-9	10 (33.3)
10-12	12 (40.0)
13-24	8 (26.7)
Median	10
Cycles of dinutuximab beta treatment, n (%)	
6	10 (33.3)
7	9 (30.0)
8	5 (16.7)
9	3 (10.0)
10	2 (6.7)
12	1 (3.3)
Median	7
Chemotherapy regimen[a] in combination with dinutuximab beta, n (%)	
Temozolomide-based chemotherapy	26 (86.7)
Platinum-based chemotherapy	13 (43.3)

[a]Patients who received both chemotherapy regimens were included. CR, complete response; MR, minor response; PD, progressive disease; PR, partial response.

immunotherapy, the CR maintenance rate was 90% (95% CI, 55.5-99.7%) after cycles beyond the standard 5, with 9 patients achieving a CR and 1 experiencing PD. The disease status of individual patients is illustrated in Fig. 2, and the detailed individual response is presented in Table SI.

Tumor response in a subgroup of patients. At the end of extended dinutuximab beta immunotherapy, among the 6 patients with relapsed NB, the ORR was 33.3% (2/6 patients) and the DCR was 66% (4/6 patients). Among these 6 patients, 1 achieved a CR, 1 achieved a PR, 2 reported SD and 2 experienced PD. Among the 24 patients with refractory NB, the ORR was 75% (18/24 patients) and the DCR was 95.8% (23/24 patients), including 14 patients who achieved a CR, 4 who achieved a PR, 5 who reported SD and 1 who had developed PD. Numerically, patients with refractory disease achieved a better tumor response compared with those with relapsed disease.

Among the 12 patients with only bone metastasis prior to the initiation of dinutuximab beta therapy, the ORR was 58.3% (7/12 patients) and DCR was 91.7% (11/12 patients). At the end of dinutuximab beta treatment, 4 patients achieved a CR, 3 achieved a PR, 4 noted SD and 1 experienced PD. For 1 patient with isolated BM metastasis, a SD state remained

Table III. Responses at cycles 3 and 5/6, and at the end of dinutuximab beta immunotherapy in 20 patients with residual active disease.

Category	After cycle 3	After cycle 5/6	After the end of immunotherapy	Best response
CR, n (%)	3 (15)	4 (20)	6 (30)	6 (30)
PR, n (%)	2 (10)	4 (20)	5 (25)	7 (35)
MR, n (%)	0 (0)	0	0	0 (0)
SD, n (%)	14 (70)	12 (60)	7 (35)	7 (35)
PD, n (%)	1 (5)	0 (0)	2 (10)	0 (0)
ORR, %	25	40	55	65
DCR, %	95	100	90	100

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; ORR, objective response rate, includes patients with complete response and partial response; DCR, disease control rate, includes patients with complete response, partial response, minor response, and stable disease.

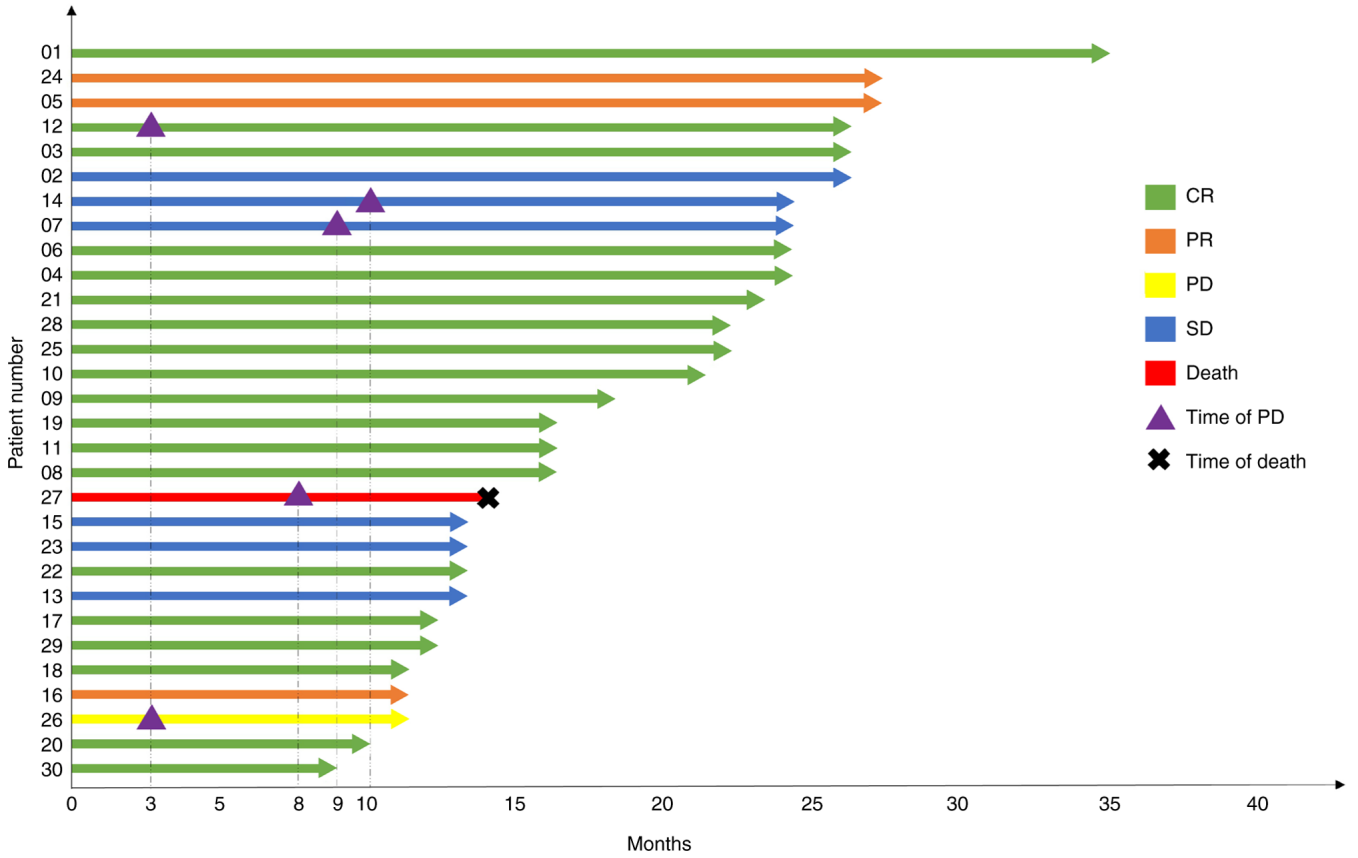

Figure 2. Waterfall plot depicting individual patient responses to treatment. Different colors indicate the tumor status at the last follow-up, CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

throughout the treatment period. Notably, it was found that a CR was achieved at the last follow-up examination after treatment cessation. It was speculated that this was due to a delayed effect associated with dinutuximab beta immunotherapy.

Additionally, 2 patients had concurrent active lesions in both bone and BM. Of them, 1 patient who initially experienced SD achieved a CR subsequently, whereas the other patient experienced PD. Among the 4 patients with concurrent active soft-tissue and bone metastases, 2 achieved a CR, 1 achieved a PR and 1 experienced SD, with an ORR of 75% (3/4 patients) and a DCR of 100.0% (4/4 patients).

The tumor status at the center was assessed using ^{18}F-NOTATATE-PET/CT imaging prior to dinutuximab beta therapy, after 3 cycles, after 5/6 cycles and at the end of the extended treatment cycles. A gradual decrease in tumor

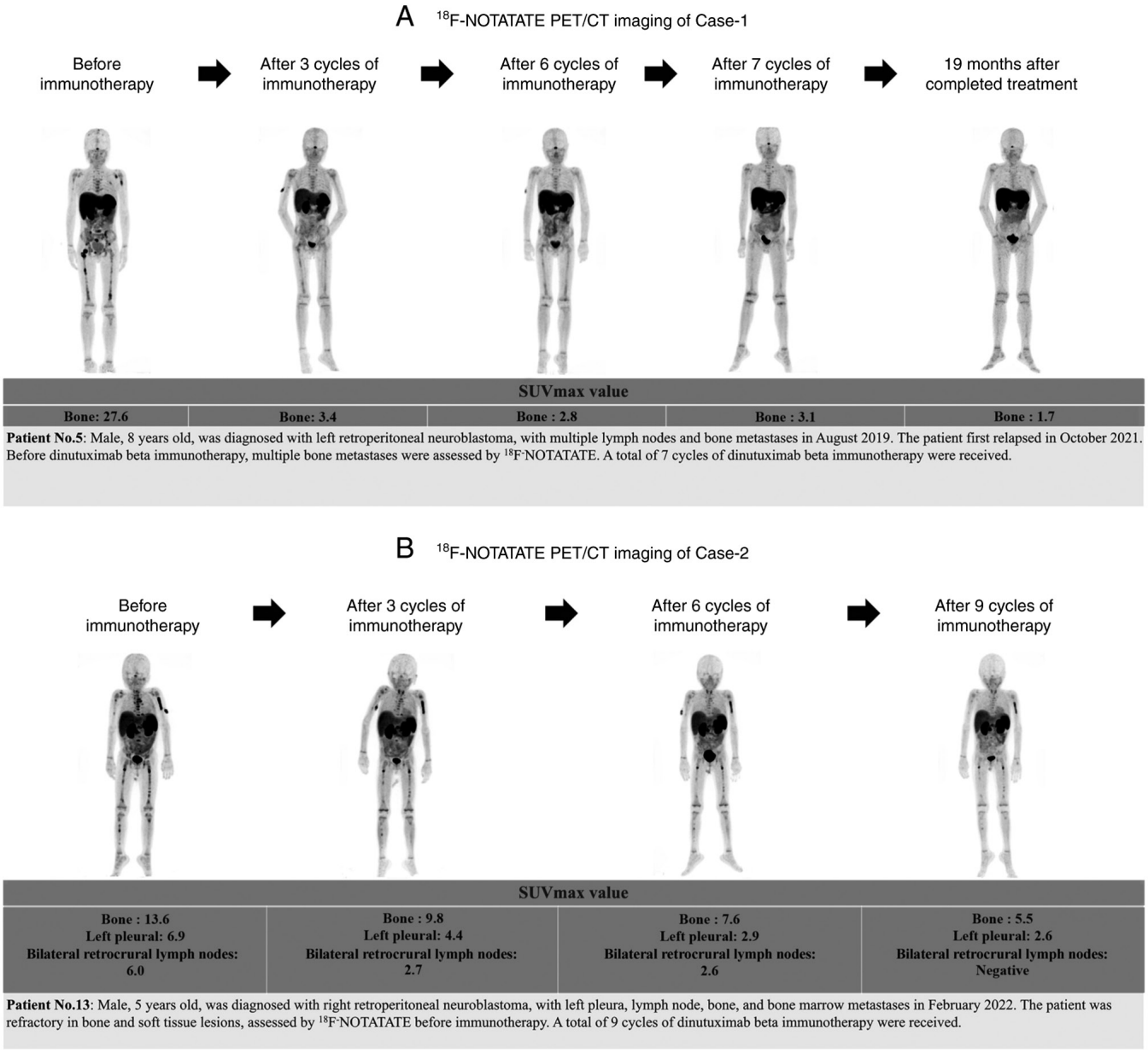

Figure 3. Assessment of immunotherapeutic efficacy based on PET-NOTATATE uptake activity. (A) Patient no. 5: A gradual reduction in SUVmax of bone metastases was observed following successive cycles of dinutuximab beta immunotherapy. (B) Patient no. 13: Decreased SUVmax values were noted across multiple metastatic sites with continued dinutuximab beta treatment, indicating treatment response. SUVmax, maximum standardized uptake value; PET/CT, positron emission tomography/computed tomography.

activity was observed with the extension of dinutuximab beta treatment cycles. Two typical cases and corresponding imaging data, which include bone or pleura/lymph node metastasis, are presented for reference in Fig. 3.

Furthermore, among the 23 patients who received a stem cell transplantation, 13 patients achieved a CR, 4 achieved a PR, 5 exhibited SD and 1 patient developed PD. The ORR and DCR were 73.9% (17/23 patients) and 95.7% (22/23 patients), respectively. Among the 7 patients who did not receive a stem cell transplantation, 2 patients achieved a CR, 1 achieved a PR, 2 exhibited SD and 2 developed PD. The ORR was 42.9% (3/7 patients) and the DCR was 71.4% (5/7 patients). It appears that patients who received a stem cell transplantation exhibited a more favorable tumor response compared with those non-transplanted patients.

Of the 4 patients with PD who received chemoimmunotherapy, 2 patients achieved a CR, 1 achieved a PR and 1 exhibited SD, with an ORR of 75% (3/4 patients) and a DCR of 100.0% (4/4 patients), suggesting the beneficial effects of chemoimmunotherapy for patients with PD. Furthermore, 2 patients developed PD after receiving 3 cycles of dinutuximab beta immunotherapy and they continued with co-therapy with a chemotherapy regimen. One of these patients was assessed as exhibiting SD after 6 cycles of dinutuximab beta treatment and subsequently achieved a PR after receiving 10 cycles. However, the other patient still had active disease after 6 cycles of dinutuximab beta. Continuing with chemoimmunotherapy may be a beneficial treatment option for patients with PD.

Survival analysis. The 2-year PFS rate was 83.2% (95% CI, 64.2-92.6%) and the 2-year OS rate was 94.7%

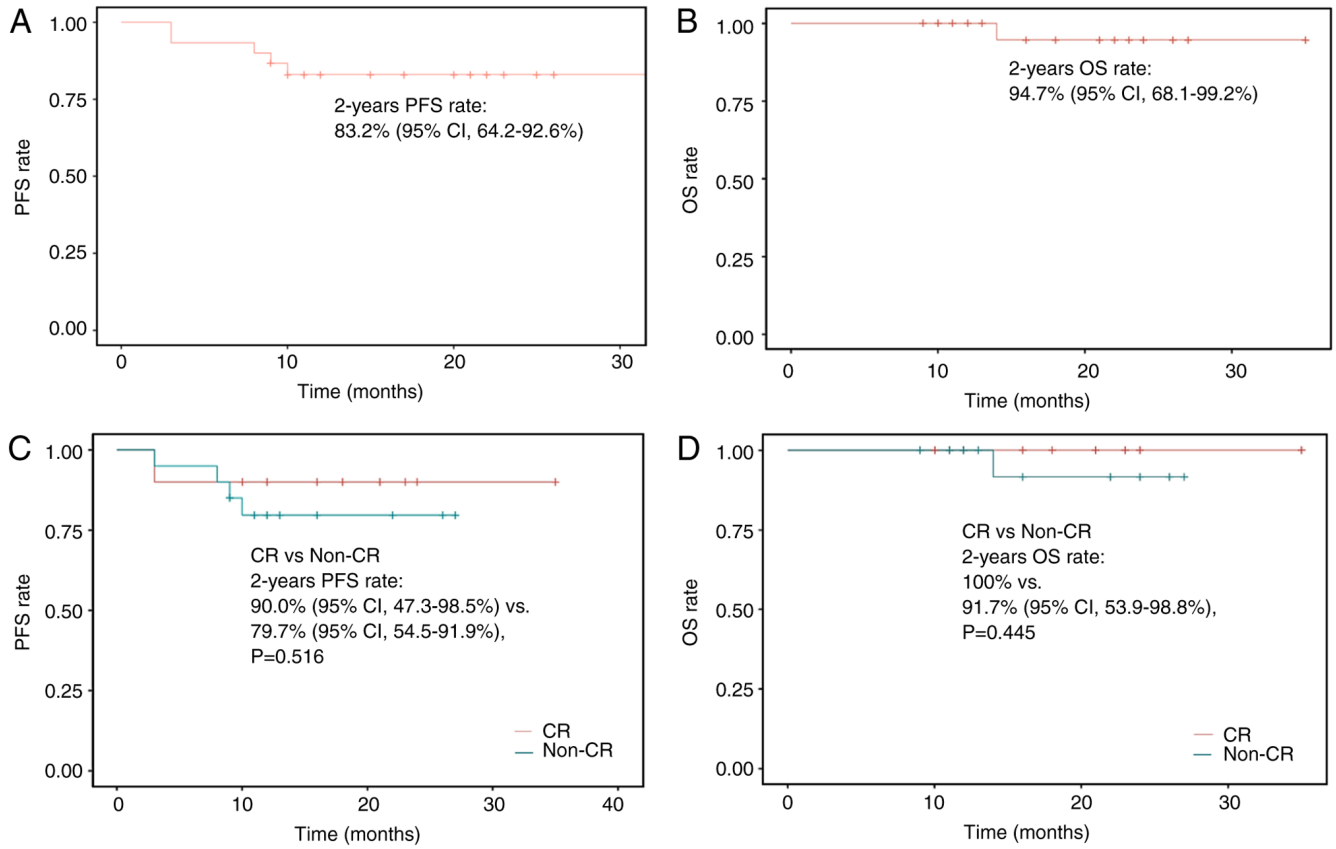

Figure 4. Kaplan-Meier survival analysis in patients with relapsed or refractory neuroblastoma. (A) PFS in all 30 patients. (B) OS in all 30 patients. (C) PFS stratified by CR vs. non-CR status prior to initiation of immunotherapy. (D) OS stratified by CR vs. non-CR status prior to initiation of immunotherapy. CR, complete response; PFS, progression-free survival, OS, overall survival.

(95% CI, 68.1-99.2%) for the overall population (Fig. 4A and B). Although not statistically significant, the 2-year PFS rate [(90.0%; 95% CI, 47.3-98.5%) vs. (79.7%; 95% CI, 54.5-91.9%); P=0.516] and the 2-year OS rate [(100.0%) vs. 91.7% (95% CI, 53.9-98.8%); P=0.445] were numerically higher in patients who achieved a CR compared with those values in patients who did not achieve a CR prior to dinutuximab beta immunotherapy (Fig. 4C and D).

The prognostic impact of clinical variables on PFS was further assessed. The model included tumor status prior to antibody therapy (CR vs. non-CR), disease type (refractory vs. relapsed) and history of autologous stem cell transplantation. MYCN amplification was excluded due to the absence of progression events in this subgroup. The analysis identified disease type as a significant predictor, with refractory NB associated with a reduced risk of progression (hazard ratio, 0.14; 95% CI, 0.02-0.92; P=0.04). Other variables did not reach statistical significance, likely due to the limited sample size and number of events. Detailed results are presented in Fig. S1.

Safety. During the standard 5 cycles of treatment, the most common grade ≥3 TRAEs were infections (n=26; 86.7%), neutropenia (n=25; 83.3%), leukopenia (n=17; 56.7%) and pain (n=16; 53.3%). These TRAEs persisted into the extended immunotherapy phase, with higher incidence rates compared with the standard cycles [infections, n=27 (90%); neutropenia, n=26 (86.7%); leukopenia, n=19 (63.3%) and pain, n=16 (53.3%)]. Nonetheless, these events were clinically manageable and did not result in treatment discontinuation. Moreover, no long-term toxicities were observed during the follow-up period. Detailed TRAEs are presented in Table IV.

Notably, the use of morphine decreased from cycle 3, showing reduced immune-related pain (Fig. 5). Furthermore, no immune-related deaths were observed.

Discussion

The present study findings suggest that cycles beyond the standard 5 cycles of dinutuximab beta treatment combined with chemotherapy improve tumor responses and survival in patients with R/R NB. A subset of patients achieved optimal responses after undergoing extended dinutuximab beta treatment cycles, contributing to favorable outcomes.

Anti-GD2 immunotherapy has shown promise for HR-NB. Dinutuximab beta, dosed at 10 mg/m^2/day for a fixed 5 cycles is recommended according to the Summary of Product Characteristics (7,18). Given the poor prognosis of R/R cases and limited effective options, extending therapy beyond 5 cycles may be a viable strategy. In a retrospective study from Poland and Germany, 31% of patients showed best responses after >5 cycles, with treatment extended up to 10 cycles (12). A Turkish study similarly reported treatment up to 14 cycles with positive outcomes (19). Consistent with these findings, the present study showed that 38.5% of patients benefited from extended treatment, with up to 12 cycles administered. Late responses were observed post-cycle 5, suggesting that residual disease may still respond to prolonged therapy. The low

Table IV. Evaluation of treatment-related adverse events (n=30).

	Period during the standard 5 cycles			Period during the extended immunotherapy cycles		
Adverse events	Grade 3, n (%)	Grade 4-5, n (%)	Total, n (%)	Grade 3, n (%)	Grade 4-5, n (%)	Total, n (%)
Anemia	15 (50.0)	0 (0.0)	15 (50.0)	15 (50.0)	0 (0.0)	15 (50.0)
Leukopenia	16 (53.3)	1 (3.3)	17 (56.7)	16 (53.3)	3 (10.0)	19 (63.3)
Neutropenia	24 (80.0)	1 (3.3)	25 (83.3)	24 (80.0)	2 (6.7)	26 (86.7)
Thrombocytopenia	10 (33.3)	3 (10.0)	13 (43.3)	10 (33.3)	6 (20.0)	16 (53.3)
Elevated serum transaminase levels	6 (20.0)	0 (0.0)	6 (20.0)	7 (23.3)	0 (0.0)	7 (23.3)
Infection	26 (86.7)	0 (0.0)	26 (86.7)	27 (90.0)	0 (0.0)	27 (90.0)
Pain	16 (53.3)	/	16 (53.3)	16 (53.3)	/	16 (53.3)
Fever	9 (30.0)	0 (0.0)	9 (30.0)	9 (30.0)	0 (0.0)	9 (30.0)
Capillary leak syndrome	2 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	2 (6.7)

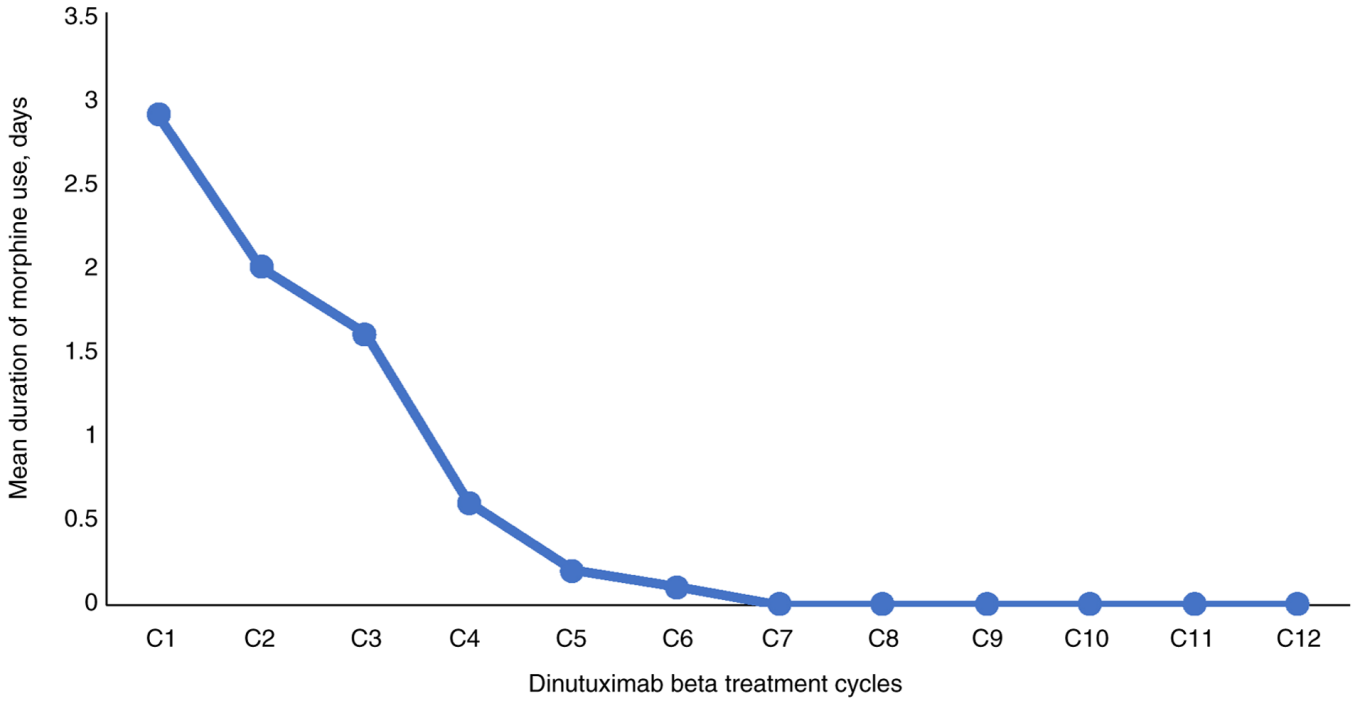

Figure 5. Mean duration of morphine use per treatment cycle in patients with relapsed or refractory neuroblastoma.

toxicity profile of dinutuximab beta supports the feasibility of extended use.

The combination of anti-GD2 antibodies with chemotherapy has enhanced efficacy in relapsed/progressive HR-NB, as demonstrated in randomized trials BEACON-Immuno and ANBL1221 (9,20). Preclinical studies also reported up to 17-fold increased cytotoxicity when dinutuximab beta was combined with chemotherapy, attributed mainly to enhanced antibody-dependent cellular cytotoxicity (21). The current study employed both platinum-based and temozolomide-based regimens. Despite no stratified analysis by regimen, dinutuximab beta showed consistent activity across all combinations. Supporting this, the SACHA-France study (clinical trial no. NCT04477681) reported comparable ORRs of 40-42% across different chemotherapy backbones, namely topotecan + cyclophosphamide, temozolomide + topotecan, and temozolomide + irinotecan when combined with dinutuximab beta, suggesting that the choice of chemotherapy may not significantly influence efficacy (22). These findings further support the notion that the choice of chemotherapeutic drugs may not significantly impact the overall efficacy of dinutuximab beta-based chemoimmunotherapy.

Dinutuximab beta was generally well tolerated in the present study, with a similar profile of grade ≥3 TRAEs as observed in the SIOPEN trials (23,24). The TRAE profile of chemoimmunotherapy in the present study, which was consistent with previous findings, indicates that the majority

of TRAEs are hematological toxicities (12,25), and that they are considered to be predominantly induced by chemotherapy. Pain is one of the most common AEs associated with anti-GD2 antibodies (26) and was well managed in the present study. Additionally, no severe neurological disturbances were observed. In the present study, a higher incidence of AEs was observed during the extended immunotherapy cycles compared with that in the standard 5-cycle treatment period. Notable increases were seen with regard to leukopenia, neutropenia, thrombocytopenia, transaminase elevations and infections. Despite the increased frequency, these events were clinically manageable with standard supportive measures, and no long-term or irreversible toxicities were documented. These findings support the feasibility and tolerability of extended chemoimmunotherapy in patients with HR-NB when administered under appropriate clinical oversight.

Although a multivariate analysis was performed to explore potential prognostic factors for PFS, its interpretability is constrained by the limited number of progression events and the modest cohort size. As such, the analysis should be viewed as exploratory and hypothesis-generating rather than confirmatory. To maintain scientific transparency, the findings have been provided as supplementary material. Ongoing follow-up and event accumulation will be critical to support more robust multivariable modeling and to validate potential prognostic indicators in this population.

Several limitations of the present study should be acknowledged. The study was a retrospective, single-center and non-randomized study, which introduces the potential for selection bias that may limit the generalizability of the findings to a broader population. The single-center nature of the study also restricts the diversity of the sample, potentially limiting the applicability of the results to other healthcare settings. The absence of a well-defined control group, such as patients receiving only the standard 5-cycle regimen, restricts the ability of the study to definitively assess the incremental benefit of extended treatment. As such, the observations should be interpreted with caution.

In conclusion, cycles beyond the standard 5 cycles of dinutuximab beta treatment in combination with chemotherapy demonstrated feasibility, tolerability and potential clinical benefit in patients with R/R NB. A subset of patients achieved meaningful responses following extended treatment, supporting the rationale for prolonged anti-GD2-based chemoimmunotherapy. However, the retrospective, single-center design and absence of a control arm limit the strength of causal inferences regarding treatment efficacy. To substantiate these findings and determine optimal treatment duration, future prospective, multi-center randomized trials are essential.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZG was responsible for organizing, validating, and maintaining data to ensure its accuracy, consistency, and usability for analysis, statistical analysis, writing the original draft, and reviewing and editing the manuscript. SK performed study conceptualization, assisted with the methodology, and reviewed and edited the manuscript. CB performed the statistical analysis and helped to write the original draft. YL and XY performed data curation, validation, statistical analysis, and manuscript review and editing. KS and YS performed investigation, literature research, study conception, and manuscript review and editing. FC performed study supervision, study conception, and manuscript review and editing. JW was responsible for conceptualization, methodology, supervision, writing the original draft, and reviewing and editing. JW and ZG confirm the authenticity of all raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shandong First Medical University and Shandong Academy of Medical Sciences (Jinan, China; approval no. SDTHEC202503192). The requirement for informed consent was exempted due to the retrospective nature of the data acquisition.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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