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A clinical observational study of dinutuximab beta as first-line maintenance treatment for patients with high-risk neuroblastoma in China

Xuedi Yu[1], Suyi Kang[1], Junjie Ge[1] and Jingfu Wang[1*]

Abstract

Background High-risk neuroblastoma (HR-NB) is associated with high metastatic and relapse rates that require intensive multimodal treatment. We evaluated the efficacy and safety of dinutuximab beta as first-line maintenance immunotherapy in pediatric patients with HR-NB in real-world clinical settings in China.

Methods We retrospectively reviewed the clinical records of pediatric patients with newly diagnosed HR-NB in the hospital from October 2021 to November 2023. Patients treated with dinutuximab beta in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin as the first-line maintenance therapy were included in this study. Among patients with residual disease after completing induction and consolidation treatment, those with partial response (PR) or very good partial response (VGPR) except for bone marrow (BM) residue were also administrated vincristine/irinotecan/temozolomide (VIT) chemotherapy.

Results Fifty-one patients with newly diagnosed HR-NB who achieved at least PR before immunotherapy were evaluated. At the end of immunotherapy, the objective response rate (ORR) in 33 patients with evidence of disease was 60.6% (95% confidence interval (CI), 42.1-77.1%) and the complete response rate (CRR; $n=18$) was 54.5% (95% CI, 36.4-71.9%). The 2-year event-free survival (EFS) rate and overall survival (OS) rate were 80.1% (95% CI, 66.2-88.8%) and 97.6% (95% CI, 84.3-99.7%), respectively. The 2-year EFS rate was higher in patients with CR (94.4%; 95% CI, 66.6-99.2%) than in non-CR patients (72.6%; 95% CI, 53.9-84.7%). Dinutuximab beta was well tolerated in patients and had fewer side effects, which decreased over time. Co-treatment of dinutuximab beta with VIT chemotherapy did not require discontinuation in patients undergoing immunochemotherapy.

Conclusion The study showed promising efficacy and safety of dinutuximab beta as the first-line maintenance immunotherapy for pediatric patients with HR-NB. Notably, the combination of dinutuximab beta with GM-CSF and VIT chemotherapy could be used for treating patients who did not achieve CR after previous multimodal therapy.

Keywords High-risk neuroblastoma, Dinutuximab beta, GD2-antibody immunotherapy, GM-CSF, First-line maintenance, Chemotherapy

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Introduction

Neuroblastoma is an extracranial solid malignancy that originates from the sympathetic nervous system. It occurs most frequently in children and accounts for 12% of pediatric cancer-related deaths [1, 2]. On the basis of the Surveillance, Epidemiology, and End Results (SEER) cancer registry database, the age-standardized incidence rate of neuroblastoma in individuals younger than 20 years is 7.8 cases per million [3]. As per the National Center for Pediatric Cancer Surveillance of China, the incidence rate of neuroblastoma in children aged 0 to 14 years is 7.72 cases per million [4]. Moreover, the National Health Commission of the People's Republic of China has officially included neuroblastoma in their list of rare diseases [5].

Neuroblastoma is a highly heterogeneous malignancy with highly variable outcomes according to risk stratification. Patients classified as having low-risk or intermediate-risk neuroblastoma show excellent prognosis with multidisciplinary therapy (with a 5-year event-free survival [EFS] rate of 90% and a 5-year overall survival [OS] rate of 95%) compared with the prognosis of high-risk neuroblastoma (HR-NB; with a 5-year EFS rate of 37.7% and 5-year OS rate of 48.9%) [6, 7]. Patients with high-risk phenotypes are associated with higher metastatic rates. Treatment strategies for pediatric patients with HR-NB are more challenging because of higher metastatic and relapse rates [8]. Furthermore, minor residual tumors after achieving remission remain a major obstacle for complete recovery because of their undetectable nature with the current testing methods.

Many tumors, including neuroblastoma, overexpress tumor-associated antigens, that is, glycosphingolipid disialoganglioside (GD2), which could be exploited for target-based immunotherapies [9, 10]. Dinutuximab beta, a human-mouse chimeric anti-GD2 monoclonal antibody [11], has shown target specificity against neuroblastoma in preclinical and early clinical studies [12, 13]. The European Medicines Agency (EMA) has approved dinutuximab beta for the treatment of HR-NB and relapsed or refractory neuroblastoma, with the aim of improving their survival rates, without granulocyte-macrophage colony-stimulating factor (GM-CSF) [14]. Dinutuximab beta has become the standard maintenance treatment for patients with HR-NB in the first-line setting who achieve at least a partial response (PR) after early multimodal treatment [13, 14]. In China, the National Medical Products Administration approved dinutuximab beta in August 2021 for the treatment of patients with HR-NB and relapsed or refractory neuroblastoma aged ≥ 12 months [15]. Another anti-GD2 monoclonal antibody, dinutuximab, similar to dinutuximab beta, was approved by the US Food and Drug Administration in 2015. A randomized controlled trial showed that dinutuximab, interleukin-2 (IL-2), GM-CSF, and isotretinoin improved outcomes in patients with HR-NB during the maintenance therapy [16]. Studies showed that GM-CSF results in increased numbers and activation of circulating neutrophils. Combining GM-CSF with dinutuximab enhances antibody-dependent cell-mediated cytotoxicity, ultimately enhancing the anti-neuroblastoma activity of anti-GD2 monoclonal antibody. Besides, GM-CSF is an M1 macrophage polarizing factor, and the expression and release of tumor necrosis factor will also be increased in the environment after chemotherapy [17–19]. Although there are no data from clinical trials about the use of GM-CSF in combination with dinutuximab beta, this cytokine was added to the treatment in light of its potential benefit derived from preclinical considerations according to the consensus reached for the treatment of HR-NB patients in China. At present, there is a paucity of data on the use of dinutuximab beta in the real-world clinical practice in China. Therefore, we conducted a study to evaluate the efficacy and safety of dinutuximab beta as the first-line maintenance therapy in pediatric patients with HR-NB, based on the clinical data from a single center.

Materials and methods

Study design and ethics

In this retrospective, observational, clinical study, pediatric patients with HR-NB receiving dinutuximab beta, GM-CSF, and isotretinoin, with or without chemotherapy, as the first-line maintenance treatment were included in this study. The clinical records of pediatric patients with HR-NB who were registered between October 2021 and November 2023 were reviewed [20].

Patients and treatment

The study included patients with newly diagnosed HR-NB who were treated with dinutuximab beta immunotherapy as the first-line maintenance treatment. Patients eligible for the study were those who had achieved a complete response (CR), very good partial response (VGPR), or PR before receiving immunotherapy; were aged ≥ 12 months; and had stage 4 neuroblastoma according to the International Neuroblastoma Staging System (INSS) or had stage 2 or 3 neuroblastoma with v-myc avian myelocytomatosis viral oncogene (MYCN) amplification according to the INSS [21].

Patients with HR-NB received the first-line treatment in 3 phases: induction treatment, consolidation treatment, and maintenance treatment. The China expert consensus about the diagnosis and treatment of pediatric neuroblastoma [22] and GD2-antibody dinutuximab beta in the treatment of neuroblastoma in children [23] were referred to design the therapy regimen of maintenance treatment. For patients who achieved CR or VGPR (minimal residual disease in bone marrow [BM] only),

dinutuximab beta, with GM-CSF and isotretinoin (regimen 1), was administered. For patients who achieved PR or VGPR (except for only BM residue), dinutuximab beta, GM-CSF, isotretinoin, and chemotherapy (regimen 2) were administered. Patients were scheduled to receive dinutuximab beta at a dose of 10 mg/m^2 once daily (o.d.) for 10 consecutive days for a total of 5 cycles given every 5 weeks with recommended supportive care. Isotretinoin was initiated 2 days after the end of dinutuximab beta therapy and was given at a dose of 160 mg/m^2/d, divided into 2 daily doses for 14 consecutive days. In total, there were 6 cycles of treatment. In regimen 1, GM-CSF treatment was started 3 days before the initiation of dinutuximab beta and was administered daily at a dose of 250 μg/m^2/d until the end of dinutuximab beta treatment (appropriated for neutrophil count $< 20 \times 10^6$/L). In regimen 2, the chemotherapeutic drugs vincristine (1.5 mg/m² for 1 day)/irinotecan (50 mg/m² for 5 days)/temozolomide (100 mg/m² for 5 days, [VIT]), combined with dinutuximab beta were administered. GM-CSF was administered at the end of the chemotherapy and until 2 days after the completion of dinutuximab beta immunotherapy (appropriated for neutrophil count $< 20 \times 10^6$/L; Regimen 1 and Regimen 2 are shown in Fig. 1).

Treatment assessments and safety

Tumor responses were routinely assessed before immunotherapy; after 3, 5, 6, 8, and 10 cycles; and at the end of dinutuximab beta immunotherapy. After the termination of the clinical treatment, tumor responses were assessed every 3 months for the first year and every 6 months for the second-third year. Tumor was assessed according to the 2017 International Neuroblastoma Response Criteria (INRC) [24], taking the tumor status before dinutuximab beta immunotherapy as baseline. The 18 F-NOTATATE method, along with positron emission tomography (PET) or computed tomography (CT), was used to evaluate bone and soft tissues in the clinical setting. Patients with BM infiltration were assessed using cytomorphologic examination and immunocytochemical staining of GD2. All assessments were performed by investigators in the study center. Adverse events (AEs) were evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analyses

The primary outcome was the objective response rate (ORR) at the end of the treatment. The secondary outcomes were 2-year EFS and OS rates, complete response rate (CRR), and safety. EFS was defined as the period from the start of dinutuximab beta therapy to the occurrence of the first relapse, disease progression, secondary malignancy, or death from any cause, or until the last contact with the patient. OS was defined as the period from the initiation of the dinutuximab beta treatment to death from any cause.

The data cutoff date was October 29, 2024. The ORR and CRR were calculated, and 95% confidence intervals (CI) were also reported. The EFS and OS were estimated using the Kaplan-Meier method. A subgroup analysis was performed based on different disease statuses, that is, CR or non-CR status before dinutuximab beta immunotherapy.

A P-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0.

Results

Patient characteristics

A total of 51 pediatric patients with HR-NB were included in this study, and none of them were lost to the follow-up. The median duration of follow-up from the initiation of immunotherapy to the cutoff day was 26 months (range, 15 – 36 months). The median age of patients at the time of diagnosis was 36 months (range, 6 – 108 months), and male patients accounted for 56.9% ($n = 29$). Most of the patients ($n = 50$; 98%) were diagnosed with INSS stage 4 neuroblastoma, whereas 1 patient (2%) had INSS stage 3 with MYCN amplification. A total of 12 patients with neuroblastoma (23.5%) had MYCN amplification, whereas 11q deletion was observed in 20 patients (39.2%). At the time of diagnosis, the most common metastatic sites observed in patients with INSS stage 4 neuroblastoma were bone ($n = 37$; 72.5%) and BM ($n = 32$; 62.7%). Nine patients (17.6%) received 2 rounds of high-dose chemotherapy followed by a peripheral blood autologous stem cell transplantation (ASCT), whereas 36 patients (70.6%) underwent a single transplantation. Six patients (11.8%) did not undergo transplantation, but they received only radiation therapy during the consolidation treatment phase (Table 1).

Before dinutuximab beta treatment, 18 patients (35.3%) achieved CR, 12 patients (23.5%) achieved VGPR (2 patients only had minimal residual BM), and 21 patients (41.2%) achieved PR. A total of 27 patients had bone metastasis only, 2 patients had BM infiltration only, and 2 patients had both bone and BM metastases. A total of 36 patients (70.6%) and 15 patients (29.4%) received 5 and > 5 cycles of dinutuximab beta immunotherapy, respectively. Regimen 1, which consisted of dinutuximab beta with GM-CSF and isotretinoin, was given to a total of 20 patients. Among them, 18 achieved CR and 2 achieved VGPR with only minimal residual BM. Regimen 2, which included dinutuximab beta, GM-CSF, isotretinoin, and VIT chemotherapy, was administered to 31 patients. Among them, 10 achieved VGPR (except for only BM residual) and 21 achieved PR (Table 1).

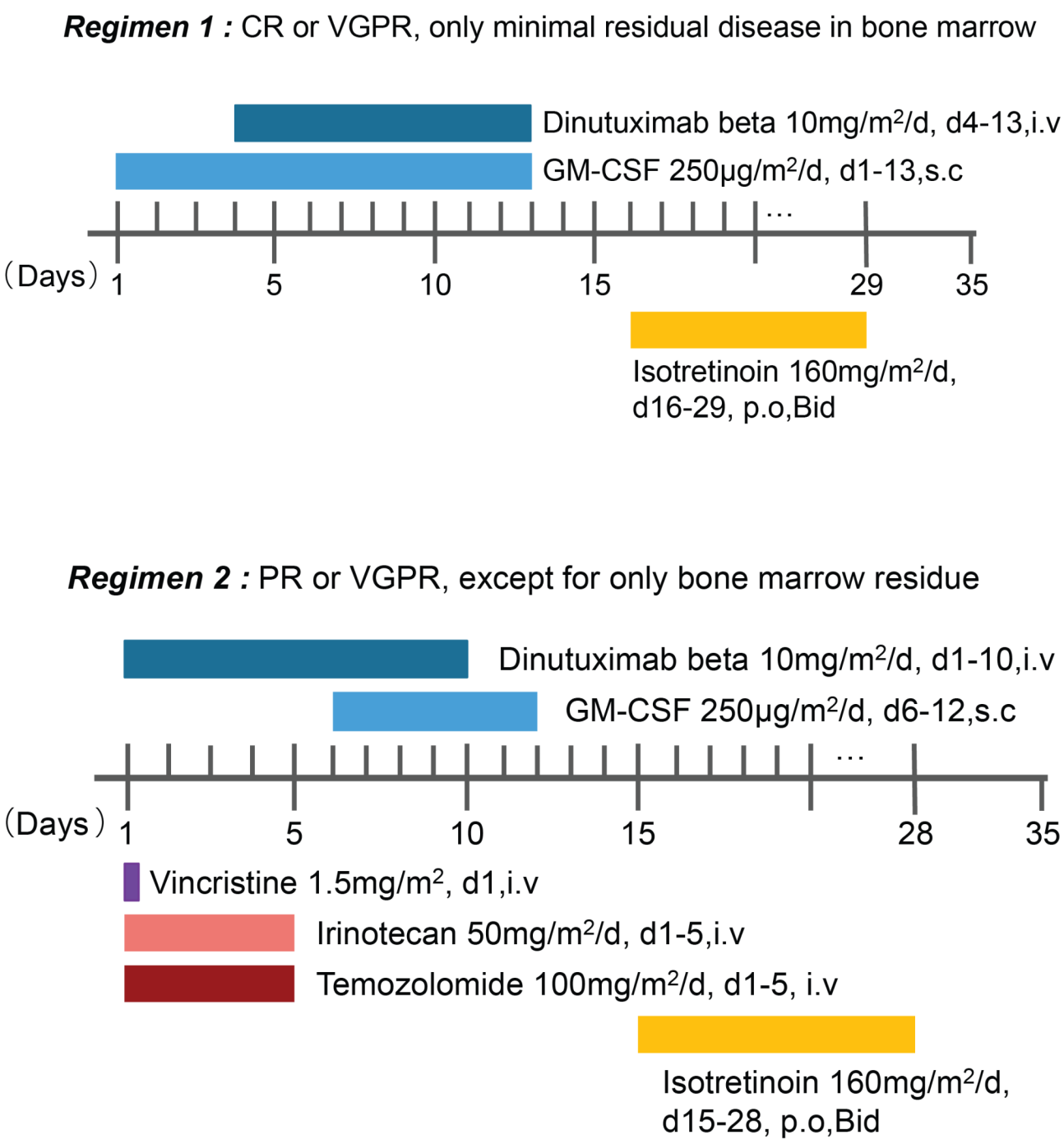

Fig. 1 Regimen 1 and regimen 2 for 51 patients as the first-line HR-NB maintenance therapy. *CR* complete response, *PR* partial response, *VGPR* very good partial response

Tumor response

The tumor response was based on patients with evidence of disease before immunotherapy. After 3 cycles of immunotherapy, the ORR was 69.7% (95% CI, 51.3-84.4%) and the CRR was 51.5% (95% CI, 33.5-69.2%). At the end of immunotherapy, the ORR was 60.6% (95% CI, 42.1-77.1%) and the CRR was 54.5% (95% CI, 36.4-71.9%). At the follow-up after 6 months, the ORR was 42.4% (95% CI, 25.5-60.8%) and the CRR was 39.4% (95% CI, 22.9-57.9%). During the observation period, the best ORR was 78.8% (95% CI, 61.1-91.0%) and the CRR was 66.7% (95% CI, 48.2-82.0%; Table 2; details on individual response is presented in Supplementary material: Table S1).

In 33 patients with evidence of disease before immunotherapy, 20 patients had tumor response, with CR in 19 patients and VGPR in 2 patients at the end of treatment.

Table 1 Patient characteristics at diagnosis and disease status before dinutuximab beta immunotherapy

Categories	Patients (*N* = 51)
Age (months)	
Median (range)	36 (6–108)
Sex, n (%)	
Male	29 (56.9%)
Female	22 (43.1%)
INSS disease stage at diagnosis, n (%)	
Stage 4	50 (98.0%)
Not stage 4[a]	1 (2.0%)
MYCN amplification, n (%)	
Amplified	12 (23.5%)
Not amplified	34 (66.7%)
Unknown	5 (9.8%)
11q loss, n (%)	
Loss	20 (39.2%)
No loss	19 (37.3%)
Unknown	12 (23.5%)
Metastatic sites at diagnosis, n (%)	
Bone	37 (72.5%)
Bone marrow	32 (62.7%)
Liver	2 (3.9%)
Treatment before dinutuximab beta immunotherapy, n (%)	
Induction chemotherapy + surgery; tandem transplant; radiotherapy	9 (17.6%)
Induction chemotherapy + surgery; single transplant; radiotherapy	36 (70.6%)
Induction chemotherapy + surgery; radiotherapy	6 (11.8%)
Site of disease at enrollment before dinutuximab beta treatment, n (%)	
Bone	27 (52.9%)
Bone marrow	2 (3.9%)
Bone and bone marrow	2 (3.9%)
Bone and soft tissues	1 (2.0%)
Soft tissues	1 (2.0%)
Status before dinutuximab beta treatment, n (%)	
CR	18 (35.3%)
VGPR[b]	12 (23.5%)
PR	21 (41.2%)
Total number of cycles, n (%)	
5	36 (70.6%)
6	6 (11.8%)
7	6 (11.8%)
9	1 (1.9%)
10	2 (3.9%)

[a]Patient had INSS stage 3 with MYCN amplification

[b]Two patients had only minimal residual BM

BM bone marrow, *CR* complete response, *INSS* International Neuroblastoma Staging System, *MYCN* v-myc avian myelocytomatosis viral oncogene, *PR* partial response, *VGPR* very good partial response

For 18 patients with no evidence of disease (CR) before immunotherapy, 14 patients (77.8%) were still in CR, whereas 1 patient had PD with newly developed bone metastases, and 3 patients were not evaluated at the end of treatment (Table 2; Supplementary material: Table S1).

In 27 patients with only bone metastasis before the initiation of dinutuximab beta treatment, the ORR at the end of immunotherapy was 63.0% (95% CI, 42.4-80.6%) and the CRR was 59.3% (95% CI, 38.8-77.6%), which included 16 patients with CR and 1 patient with VGPR. In this study, there were only 4 patients with BM involvement before starting immunotherapy with dinutuximab beta, as determined by immunocytology and immunohistochemistry. Three patients were assessed at the end of immunotherapy, of which, 2 patients were negative in BM and one patient remained positive. However, when we evaluated the best response in the BM, also including mid evaluation time points, the response rate was 100%.

Before the initiation of dinutuximab beta treatment, 29 transplantation patients with evidence of disease had an ORR of 58.6% (95% CI, 38.9-76.5%) and a CRR of 51.7% (95% CI, 32.5-70.6%), whereas in 23 single transplantation patients, the results showed an ORR of 56.5% (95% CI, 34.5-76.8%) and a CRR of 52.5% (95% CI, 30.6-73.2%). Of 6 tandem transplantation patients, 3 patients achieved CR and 1 patient achieved VGPR; of 4 non-transplantation patients, 3 patients achieved CR.

Survival analyses

After the maintenance treatment with dinutuximab beta, the 2-year EFS rate was 80.1% (95% CI, 66.2-88.8%; Fig. 2a). The 2-year OS rate was 97.6% (95% CI, 84.3-99.7%; Fig. 2b). Patients with CR tended to have numerically higher 2-year EFS rate (94.4%; 95% CI, 66.6-99.2%) compared with non-CR (VGPR and PR) patients (72.6%; 95% CI, 53.9-84.7%; $P = 0.073$; Fig. 2c). In addition, patients with CR tended to have numerically higher 2-year OS rate with 100%, compared with non-CR patients with 96.4% (95% CI, 77.2-99.5%; $P = 0.480$), although not statistically significant. It is suggested that patients who achieved CR before dinutuximab beta maintenance treatment may have a favorable advantage over those who have not achieved CR.

Safety

Dinutuximab beta was generally well tolerated with manageable clinically relevant AEs (Fig. 3a). The incidence of AEs was higher in the first treatment cycle, which gradually reduced during the subsequent treatment cycles. No AEs of grade 5 were reported; however, 1 AE of grade 4, that is, capillary leak syndrome (CLS), was observed. An analysis of the groups of patients treated with different regimens (regimen 1 or 2) showed that the types and frequency of AEs in the combination chemotherapy group

Table 2 Tumor response in patients with HR-NB who received dinutuximab beta as the first-line maintenance therapy

Evaluation time point		18 patients with no evidence of disease before immunotherapy	33 patients with evidence of disease before immunotherapy		Response rate in patients with evidence of disease
		CR (*n* = 18)	VGPR[a] (*n* = 12)	PR (*n* = 21)	
After 3 cycles of treatment (*N* = 51)	CR	18	**8**	**9**	ORR[b]: **69.7%** (23/33; 95% CI 51.3%-84.4%) CRR: **51.5%** (17/33; 95% CI 33.5%-69.2%)
	VGPR	0	0	**3**	
	PR	0	0	**3**	
	SD	0	4	5	
	PD	0	0	1	
	Not evaluated	0	0	0	
End of treatment (*N* = 51)	CR	14	**9**	**9**	ORR[b]: **60.6%** (20/33; 95% CI 42.1%-77.1%) CRR: **54.5%** (18/33; 95% CI 36.4%-71.9%)
	VGPR	0	0	**2**	
	PR	0	0	0	
	SD	0	1	4	
	PD	1	1	1	
	Not evaluated	3	1	5	
6 months follow-up (*N* = 51)	CR	10	**7**	**6**	ORR[b]: **42.4%** (14/33; 95% CI 25.5%-60.8%) CRR: **39.4%** (13/33; 95% CI 22.9%-57.9%)
	VGPR	0	0	**1**	
	PR	0	0	0	
	SD	0	0	1	
	PD	0	0	2	
	Not evaluated	8	5	11	
Best response rate in patients with evidence of disease					ORR[b]: **78.8%** (26/33; 95% CI 61.1%-91.0%) CRR: **66.7%** (22/33; 95% CI 48.2%-82.0%)

[a]Included 2 patients with VGPR receiving regimen 1, with only minimal residual disease in BM

[b]The ORR includes patients with CR, VGPR, and PR

BM bone marrow, *CI* confidence interval, *CR* complete response, *CRR* complete response rate, *HR-NB* high-risk neuroblastoma *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease, *VGPR* very good partial response

of regimen 2 (Fig. 3c) were higher than those in regimen 1 (Fig. 3b). Detailed information is presented in Supplementary material: Table S2, S3, and S4.

From the clinical practice perspective, the AEs of greatest concern were fever, pain, CLS, and ocular symptoms. Grade 3 fever (*n* = 9; 17.6%) was only observed in the first cycle. Grade 1/2 fever was observed in 47.1% of patients in cycle 1, which gradually decreased to 0 in cycle 5. Twelve patients (23.5%) reported grade 1/2 pain in cycle 1, and 4 patients (7.8%) reported grade 3 pain (not severe). In most patients, the early administration of gabapentin and continuous infusion of morphine (0.02–0.05 mg/kg/h) successfully prevented pain. The infusion of morphine was discontinued from cycle 4, and only oral gabapentin was given as prophylaxis. None of the patients discontinued the treatment with dinutuximab beta because of pain.

CLS was reported in 9 patients (17.6%) during the first cycle of the treatment; grade 3 CLS was developed in 3 patients (5.9%), whereas grade 4 CLS was observed in 1 patient (2%; symptoms of hypotension, ascites, oliguria, and other related conditions); however, it was not observed after 3 cycles. Patients with grade 3/4 CLS discontinued dinutuximab beta treatment and recovered after supportive treatment; for example, in a patient with grade 4 CLS, we discontinued the current cycle of dinutuximab beta treatment and drained the ascites and used human albumin, hydroxyethyl starch, steroid hormones and diuretics, and so on. As a result, significant improvements were observed and the patient was gradually cured. The subsequent cycles of dinutuximab beta were well tolerated in patients with CLS. In patients who developed grade 3/4 CLS, dinutuximab beta therapy was reinitiated with a lower dose, which was gradually increased in the subsequent cycles until the desired dose was reached.

One patient (2%) exhibited grade 2 ocular AEs with symptoms of decreased vision, mydriasis, and photophobia. However, the patient did not experience further visual deterioration during an extended course of treatment, and a gradual resolution of symptoms was observed 6 months after the end of treatment. The same

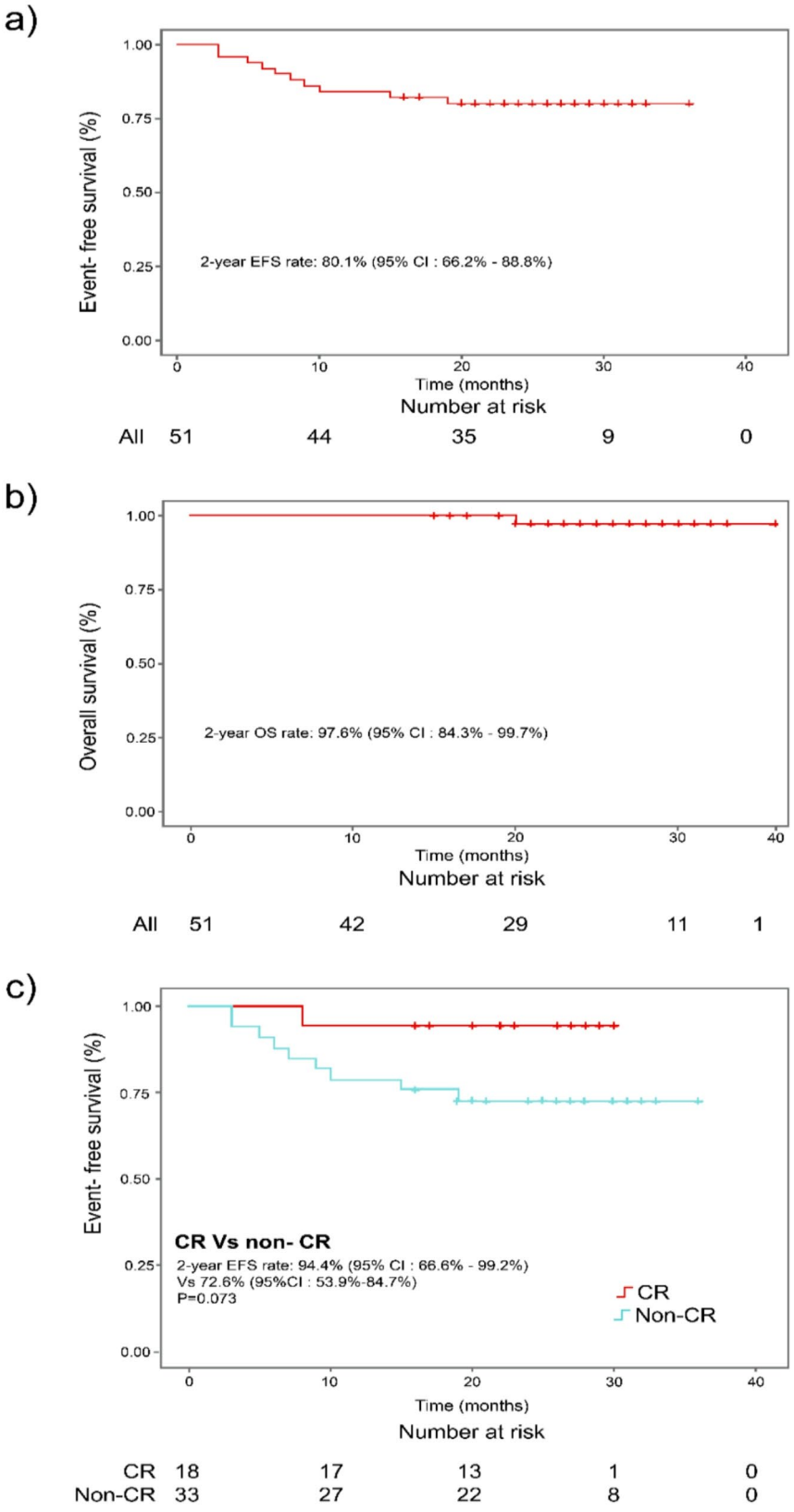

Fig. 2 Kaplan-Meier analysis: (**a**) EFS in 51 patients with HR-NB treated with dinutuximab beta immunotherapy. (**b**) OS in 51 patients with HR-NB treated with dinutuximab beta immunotherapy. (**c**) Data were shown for EFS in patients with CR versus non-CR (VGPR* + PR). * Included 2 patients with VGPR receiving regimen 1, with only minimal residual disease in bone marrow. *CI* confidence interval, *CR* complete response, *EFS* event-free survival, *OS* overall survival, *PR* partial response, *VGPR* very good partial response

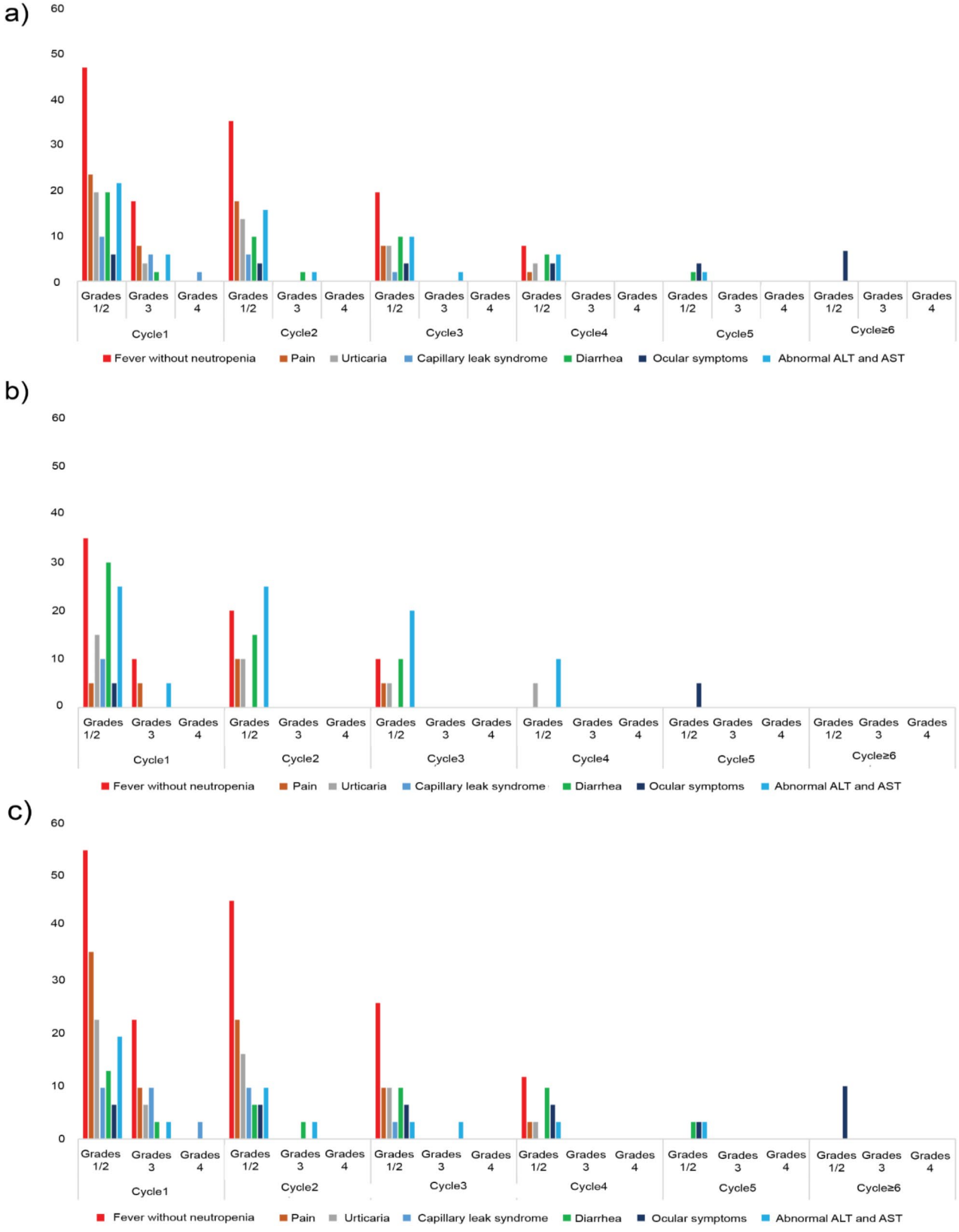

Fig. 3 Adverse events in (**a**) 51 patients, (**b**) patients treated with regimen 1, and (**c**) patients treated with regimen 2. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

patient also developed grade 3 urticaria during the first cycle of dinutuximab beta treatment. Moreover, another patient developed grade 1 ocular AEs after receiving 4 cycles of dinutuximab beta treatment. The symptoms included papilledema, mydriasis, and mild photophobia. However, there was no worsening of symptoms after the continuation of dinutuximab beta treatment.

No serious neurologic AEs were observed in this study. Other AEs included liver dysfunction, diarrhea, and urticaria. These AEs were primarily graded as 1/2 and did not require any temporary discontinuation of the treatment. No deaths related to dinutuximab beta treatment were reported.

Discussion

This retrospective study aimed to investigate the efficacy and safety of dinutuximab beta as the first-line maintenance treatment in pediatric patients with newly diagnosed HR-NB in the real-world clinical practice in China. The study demonstrated that dinutuximab beta immunotherapy was associated with encouraging tumor response and survival benefits with good treatment tolerance.

Dinutuximab beta–based immunotherapy as the first-line maintenance therapy has improved the survival rate of patients with HR-NB, as mentioned in the International Society of Pediatric Oncology Europe Neuroblastoma group HR-NB 1 trial (HR-NBL1/SIOPEN) [25]. It was reported that 2-year EFS and OS rates of 65% and 77%, respectively, in patients with HR-NB receiving dinutuximab beta as the first-line maintenance therapy combined with isotretinoin [25]. Regarding the tumor response of immunotherapy, the SIOPEN randomized clinical trial reported an ORR of 44% in patients with HR-NB [26]. In the current study, we observed a 2-year EFS rate of 80.1%, a 2-year OS rate of 97.6%, an ORR of 60.6%, and a CRR of 54.5% at the end of immunotherapy. A combination of dinutuximab beta with GM-CSF and VIT chemotherapy in non-CR patients could explain the difference in our observation cohort. Furthermore, the prognosis could be influenced by disease status before immunotherapy in the study. Patients with CR before immunotherapy exhibited a better survival rate compared with non-CR patients [25, 27]. Our findings also showed this tendency, especially in the EFS outcomes. The administration of standard treatment to reduce the tumor burden before the initiation of dinutuximab beta might be associated with a more favorable prognosis.

Chemotherapy combined with dinutuximab beta immunotherapy might be beneficial for some specific patients with HR-NB. The BEACON-Immuno study, a randomized controlled trial, evaluated the efficacy of combining anti-GD2 antibody dinutuximab beta with chemotherapy in patients with relapsed or refractory HR-NB. This combination of dinutuximab beta with temozolomide-based chemotherapy showed promising outcomes, resulting in a 30% increase in the 1-year progression-free survival (PFS) and a 17% increase in the ORR [28]. In another study, a cohort of 25 patients with relapsed or refractory HR-NB who were treated with irinotecan/temozolomide chemotherapy in combination with dinutuximab beta was analyzed. It resulted in ORR of 64% and CRR of 32% [29]. The National Comprehensive Cancer Network Clinical Practice Guidelines in Neuroblastoma (version 1.2024) recommended that bridging therapy (combining anti-GD2 monoclonal antibody with chemotherapy) to improve response may be appropriate in patients who did not achieve CR depending on the disease status at the end of induction therapy [30]. In China, an expert consensus on neuroblastoma treatment using the anti-GD2 antibody dinutuximab beta was published in 2022 [23], which suggested the regimen containing dinutuximab beta combined with VIT chemotherapy and GM-CSF for HR-NB patients with PR or stable disease (SD) after earlier standardized treatment. On the basis of the consensus, patients who did not achieve CR received dinutuximab beta in combination with VIT chemotherapy and exhibited encouraging efficacy and safety with low toxicity.

According to the recommendations in the SIOPEN treatment strategy and instructions for use of the drug [26, 31], dinutuximab beta was administered for a fixed 5 cycles of immunotherapy; however, a treatment duration exceeding 5 cycles has been observed in the real-world clinical practice. An earlier study showed that approximately 31% of patients with refractory and relapsed HR-NB achieved the best response after >5 cycles; the additional treatment cycles were given in those who were responding to therapy but had not yet achieved CR, suggesting that patients may benefit from prolonged treatment with dinutuximab beta immunotherapy [29]. Considering the tolerability and safety profile of dinutuximab beta, additional cycles (up to 10 cycles) were also administered for patients who did not achieve CR even after 5 cycles of treatment in our center. It showed a continuous reduction in tumor burden during treatment. No chemotherapy was provided during these additional cycles, which resulted in good tolerance.

Metaiodobenzylguanidine (MIBG) labeled with ^{131}I is a useful imaging scan to assess for metastatic disease in patients with neuroblastoma, however, it is not widely available in China. This study mainly uses 18 F-NOTATATE as a method to evaluate both bone and soft tissues, and the evaluation standards are consistent with the 18 F-PET/CT in the 2017 version of INRC [24]. Studies have shown that 18 F-NOTATATE can be used for the diagnosis and staging of neuroendocrine carcinoma (NET)-expressing somatostatin receptor-2 receptors, and it is a valuable diagnostic technology [32, 33].

18 F-NOTATATE has good biodistribution properties and safety, with a high tumor to background ratio for NET lesions, thereby making it a promising radioactive tracer [32, 34, 35]. Multiple studies have shown that the NET detection rate of 18 F-NOTATATE is highly consistent with that of 68Ga-DOTATATE and can be used for clinical staging [35–38].

While comparing the safety results of this study with those of the previous study on long-term, continuous infusion of single-agent dinutuximab beta [39], a higher frequency of fever, allergic reactions, and CLS was observed, which may be caused by GM-CSF. Pain was well tolerated by Chinese patients, and the initial dosage of morphine (0.015–0.02 mg/kg/h) for some patients was lower than the recommended dose, especially in the second and third cycles. Most AEs were manageable with standard supportive care; overall, the tolerability of dinutuximab beta improved with each subsequent treatment cycle.

The limitations of this study include its retrospective nature, lack of a control group, and short duration of follow-up. As a retrospective study, the number of immunochemotherapy cycles patients received was mostly based on clinical decisions, which truly reflected the clinical practice. These current results observed in this study are encouraging, and further follow-up will still be conducted in the future.

Conclusions

Multimodal treatment involving dinutuximab beta demonstrated encouraging efficacy and tolerable safety as the first-line maintenance therapy for pediatric patients with HR-NB in China. The findings of this study indicate that a combination of dinutuximab beta with GM-CSF and VIT chemotherapy could be used for patients who did not achieve CR after previous multimodal therapy in the real-world clinical practice.

Abbreviations

AE	Adverse Events
ASCT	Autologous Stem Cell Transplantation
BM	Bone Marrow
CLS	Capillary Leak Syndrome
CR	Complete Response
CRR	Complete Response Rate
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EFS	Event-Free Survival
EMA	European Medicines Agency
GD2	Glycosphingolipid Disialoganglioside
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HR-NB	High-Risk Neuroblastoma
IL-2	Interleukin-2
INRC	International Neuroblastoma Response Criteria
INSS	International Neuroblastoma Staging System
MIBG	Metaiodobenzylguanidine
MYCN	v-myc Avian Myelocytomatosis Viral Oncogene
NET	Neuroendocrine Carcinoma
ORR	Objective Response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PR	Partial Response
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
VGPR	Very Good Partial Response
VIT	Vincristine/Irinotecan/Temozolomide

Supplementary Information

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Supplementary Material 1

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Author contributions

Guarantor of integrity of the entire study- JW; study concepts and design- JW; literature research- JG, SK, XY, JW; clinical studies- JG, SK, XY, JW; experimental studies / data analysis- SK, XY; statistical analysis- SK, XY; manuscript preparation- JG, SK, XY, JW; manuscript editing- JG, SK, XY, JW. All authors read and approved the final manuscript.

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Data availability

The raw data supporting the conclusions of this article will be made available by the authors on request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Cancer Hospital Affiliated to Shandong First Medical University (approval number: SDTHEC2024001017). Informed consent was waived as it is a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Not applicable.

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