Received: 1 April 2021 | Revised: 30 April 2021 | Accepted: 3 May 2021

DOI: 10.1002/pbc.29121

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

Naxitamab combined with granulocyte-macrophage colony-stimulating factor as consolidation for high-risk neuroblastoma patients in complete remission

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Abstract

Background: Naxitamab is a humanized anti-disialoganglioside (GD2) monoclonal antibody approved for treatment of bone/bone marrow refractory high-risk neuroblastoma (HR-NB). Compassionate use (CU) expanded access program at Hospital Sant Joan de Deu permitted treatment of patients in complete remission (CR). We here report the survival, toxicity, and relapse pattern of patients in first or second CR treated with naxitamab and sargramostim (GM-CSF).

Procedure: Seventy-three consecutive patients with HR-NB (stage M at age >18 months or MYCN-amplified stages L1/L2 at any age) were treated in first or second CR. Treatment comprised five cycles of subcutaneous (SC) GM-CSF for 5 days at 250 $\mu g/m^2$/day (days −4 to 0), followed by naxitamab + SC GM-CSF for 5 days at 500 $\mu g/m^2$/day (days 1–5). Naxitamab was infused over 30 minutes at 3 mg/kg/day, days 1, 3, and 5, outpatient.

Results: Fifty-five patients were in first CR and 18 in second CR. Seventeen patients had MYCN-amplified NB and 11 detectable minimal residual disease in the bone marrow. Fifty-eight (79.5%) patients completed therapy. Four (5%) experienced grade 4 toxicities and 10 (14%) early relapse. Three-year event-free survival (EFS) 58.4%, 95% CI = (43.5%, 78.4%) and overall survival (OS) 82.4%, 95% CI = (66.8%, 100%). First CR patients 3-year EFS 74.3%, 95% CI = (62.7%, 88.1%), and OS 91.6%, 95% CI = (82.4%, 100%). EFS is significantly different between first and second CR ($p = .0029$). The pattern of relapse is predominantly (75%) of an isolated organ, mainly bone (54%). Univariate Cox models show prior history of relapse as the only statistically significant predictor of EFS but not OS.

Conclusions: Consolidation with naxitamab and GM-CSF resulted in excellent survival rates for HR-NB patients in CR.

Abbreviations: ADCC, antibody-dependent cell cytotoxicity; ASCT, autologous stem cell transplant; B/BM, bone/bone marrow; cis-RA, cis-retinoic acid; CMC, complement mediated cytotoxicity; COG, Children's Oncology Group; CR, complete remission; EFS, event-free survival; FDA, Food and Drug Administration; FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography (PET); GD2, disialoganglioside; GM-CSF, sargramostim; HR-NB, high-risk neuroblastoma; HSJD, Hospital Sant Joan de Déu; IL-2, interleukin-2; MIBG, ^{123}I-metaiodobenzylguanidine; MoAb, monoclonal antibody; MRD, minimal residual disease; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; SC, subcutaneous; SIOPEN, Societe Internationale d'Oncologie Pediatrique Europa Neuroblastoma.

KEYWORDS
anti-GD2 immunotherapy, consolidation, GM-CSF, high risk, naxitamab, neuroblastoma

1 | INTRODUCTION

The cure of high-risk neuroblastoma (HR-NB) patients remains a significant challenge worldwide. Current treatment approaches within the major international cooperative groups comprise a backbone of intensive induction chemotherapy, consolidation with high-dose chemotherapy and autologous stem cell transplant (ASCT), and dinutuximab-based immunotherapy plus cis-retinoic acid (cis-RA). Long-term survival rates for children with HR-NB are currently 40–55% in large cooperative group studies.[1–5] The latest report from a cooperative group study of the pre anti-disialoganglioside (GD2) immunotherapy era is from the German Pediatric Oncology and Hematology (GPOH) trial NB 2004.[6] This study (run from 2004 to 2016) reports a 3-year event-free survival (EFS) and overall survival (OS) of ≈33% and 52%, respectively.

Two anti-GD2 antibody families have been tested clinically in NB, 3F8, and 14.18.[7] Chimeric (ch) 14.18 was derived from the variable region of the murine monoclonal antibody (MoAb) 14.18 showing antibody-dependent cell cytotoxicity (ADCC) and complement mediated cytotoxicity (CMC) of NB and melanoma cells in vivo. Based on encouraging clinical responses in phase 1 studies, ch14.18 was tested further as consolidation therapy for HR-NB.[1] In 2001, the Children's Oncology Group (COG) initiated a randomized phase 3 trial to study the efficacy of the combination of ch14.18 (dinutuximab) with sargramostim (GM-CSF) and interleukin-2 (IL-2) in preventing NB relapse in patients in complete remission (CR) after ASCT. In 2010, the results of the COG ANBL0032 trial were published demonstrating for the first (and only) time in a randomized trial in NB significant improvement in OS and EFS.[8,9] In 2009, the Societe Internationale d'Oncologie Pediatrique Europa Neuroblastoma (SIOPEN) group designed a randomized trial to allow HR-NB patients to receive dinutuximab beta with or without IL-2 with all patients receiving oral cis-RA.[10] The analysis showed superior EFS and OS when dinutuximab beta-based immunotherapy was included compared to the same trial with only cis-RA. Patients treated in the immunotherapy cohort had 2-year EFS of 68% compared to 54% in the preimmunotherapy cohort.[10] The trial also showed that the addition of subcutaneous (SC) IL-2 to dinutuximab beta did not improve outcome, but increased toxicity. Dinutuximab-based immunotherapy is now part of the standard of care for HR-NB, at least in the limited areas of the world (North America, Western Europe, Australia, and scarcely other regions) where it is available.

Murine 3F8 (m3F8) is a murine IgG3 MoAb specific for GD2 that also induces cell death and mediates efficient ADCC and CMC against NB in vitro.[11] m3F8 was the first anti-GD2 administered to a NB patient in 1987.[7] Given the activity of m3F8 against chemo-resistant BM disease, its use was expanded to patients in their first remission with encouraging results.[10] Retrospective analysis of consecutive trials performed at Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated that m3F8 + GM-CSF + cis-RA was mainly effective against chemotherapy-resistant BM minimal residual disease (MRD).[12]

Humanization (hu) of m3F8 was undertaken with the idea to circumvent human anti-mouse antibody response, to enhance ADCC, and to reduce dosing and pain. In vitro comparison with m3F8 and dinutuximab in binding, cytotoxicity, and cross-reactivity assays showed that hu3F8 had an improved pharmacokinetic profile.[13] Similar to m3F8, hu3F8 inhibited tumor cell growth in vitro, while cross-reactivity with other gangliosides was comparable to that of m3F8. Moreover, all types of cells that induced ADCC with hu3F8 resulted more potent than m3F8, whereas CMC was reduced. Importantly, antitumor effect against NB xenografts was better with hu3F8 than m3F8.[13] In summary, humanizing m3F8 produced a next generation of anti-GD2 antibodies with substantially more potent ADCC in vitro and antitumor activity in vivo. Phase 1 and 2 clinical trials of hu3F8 have shown the effectiveness of hu3F8 + GM-CSF against chemotherapy-resistant bone/bone marrow (B/BM) disease, which prompted a fast record Food and Drug Administration (FDA) approval of hu3F8 (naxitamab; Danyelza) in November 2020.[14]

First human infusion of naxitamab produced by Ymabs Therapeutics in combination with GM-CSF was performed on June 12, 2017 at Hospital Sant Joan de Déu (HSJD). Since then patients seeking consolidation at HSJD with naxitamab and GM-CSF in the registration phase 2 international trial were screened and if not eligible because in CR, received treatment under the compassionate expanded access program (Ymabs Therapeutics) of the drug. In this report, we evaluated survival, toxicity, and pattern of relapse among HR-NB patients in first or second CR treated with naxitamab and GM-CSF and no cis-RA. Models were built to test for prognostic variables that could influence clinical outcome.

2 | MATERIALS AND METHODS

We report on 73 consecutive patients in CR treated at HSJD with naxitamab and GM-CSF from June 2017 until August 2020. This study included all patients with HR-NB (stage M at age >18 months or MYCN-amplified stages L1/L2 at any age) to consolidate first CR or second CR following induction regimens with at least three cycles of multidrug chemotherapy including alkylators and platinum-containing compounds and surgery, with/without ASCT and radiotherapy.

Patients received immunotherapy if CR was demonstrated in the extent of disease workup performed at HSJD, diagnosis was centrally reviewed, and major organ toxicity was grade <2 by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Informed written

consents for treatments and tests were obtained according to HSJD institutional review board rules.

Naxitamab-based immunotherapy cycles comprised priming doses of SC GM-CSF for 5 days at 250 $\mu g/m^2$/day (days −4 to 0), followed by naxitamab + SC GM-CSF for 5 days at 500 $\mu g/m^2$/day (days 1–5). Naxitamab was infused intravenous (IV) over 30 minutes, at 3 mg/kg/day on days 1, 3, and 5, for a total dose of 9 mg/kg (~270 mg/m^2) per cycle. GM-CSF was not given if the ANC was >20,000/μl. Treatment cycles were repeated every 4 weeks (±1 week) for a total of five cycles. Naxitamab treatment was given outpatient for all cases.

Radiation to the primary site and bulky sites at diagnosis was administered either before immunotherapy, after induction phase (chemo and surgery and ASCT for those who had received it), or after immunotherapy at the end of consolidation phase (immunotherapy and radiation).

All patients received daily oral supplementation of docosahexaenoic acid triglyceride (DHA-TG) at 0.25 g/kg, half administered in a single oral intake and the rest in the other two administrations during the day, matched with meals. None of the patients received cis-RA.

Adverse events were prospectively collected and reported in parallel to authorities and to Ymabs, according to the established contract between HSJD and Ymabs Therapeutics for the drug expanded access program. CTCAE version 4.0 was used for reporting.

2.1 | Disease evaluations

Disease status was assessed by histology of BM aspirates obtained from bilateral posterior and bilateral anterior iliac crests, ^{123}I-metaiodobenzylguanidine (MIBG) SPECT scan, and whole-body magnetic resonance imaging (MRI). Fluorodeoxyglucose (FDG)-positron emission tomography (PET) was used for MIBG non-avid cases at diagnosis. Disease response was defined according to the revised International Neuroblastoma Response Criteria (INRC).[15] Four BM aspirates and ^{123}I-MIBG/FDG-PET scans were performed after cycles 2 and 5 in all patients to assess response. Treatment could be continued if CR was maintained after two cycles for a total of five cycles.

Quantitative reverse transcription-polymerase chain reaction was used to assess MRD, as described,[16] in BM before treatment and after every two cycles of immunotherapy. During follow-up, disease status was assessed every 3 months for 2 years by histology of BM aspirates (×4) and MRD plus ^{123}I-MIBG/FDG-PET scans, and once a year craniospinal MRI.

2.2 | Statistical analysis

Continuous variables were described using the median, minimum, and maximum. Categorical variables were described using absolute frequencies and percentages. EFS was defined as time from start of immunotherapy to progressive disease (PD), relapse, secondary malignancy, or toxic death, and was censored at last follow-up in the absence of these events. OS was defined as time from start of immunotherapy to death and was censored at last follow-up if death did not occur. The Kaplan–Meier method[17] was used to estimate the EFS and OS curves. Prognostic impact of clinical and biological features on EFS and OS was tested by the log-rank test.[18] Optimal cut-offs for age were estimated using the Contal–O'Quigley method,[19] with OS as outcome. Cox models were used to derive hazard ratios for clinical and biological features on EFS and OS.

3 | RESULTS

A total of 73 HR-NB patients were treated with naxitamab and GM-CSF in first or second CR after full workup was performed at HSJD. Fifty-five patients were in first CR and 18 in second CR. Among patients in second CR, seven had a history of isolated central nervous system (CNS) relapse including one with CNS and systemic relapse, and 11 prior systemic relapse. Table 1 describes the clinical characteristics of all patients treated, separated by first or second CR cohorts. Median age for the whole group at diagnosis was 3.2 years and age at immunotherapy initiation 4.5 years. Seventeen of the patients had MYCN-amplified tumors. Twenty-two of the 73 patients had ASCT, 10 (18%) of the 55 in first CR and 12 (67%) of the 18 in second CR. Eleven patients had positive/detectable BM MRD before immunotherapy. None of the patients had received anti-GD2 MoAb previously.

Overall, a total of 385 cycles of naxitamab and GM-CSF were administered. Fifty-eight of the 73 patients completed planned five cycles, whereas 15 (20%) did not. Among the 15 patients who did not complete planned treatment, four experienced grade 4 toxicities including two apnea induced by naxitamab on days 1 and 3 of first cycle; one opioid related chest rigidity syndrome on days 1 and 3 of first cycle, and one stroke after completing the first cycle unlikely related to naxitamab. One patient developed elevated HAHAs that interrupted planned treatment after two cycles. In this patient, HAHAs were found retrospectively to be elevated above normal (1300 U/ml) from baseline before naxitamab infusion. While therapy was stopped, this patient relapsed in the CNS. Ten patients did not complete treatment because of early relapse, six of the 55 patients in first CR, and four of the 18 patients in second CR.

Patients who maintained CR at the end of the five cycles of immunotherapy did not receive any further treatment. Figure 1 shows the Kaplan–Meier curves for the whole population with 2-year OS of 90.6%, 95% CI = (82.5%, 99.5%) and 3-year OS of 82.4%, 95% CI = (66.8%, 100%). Two-year EFS of 65.7%, 95% CI = (54.8%, 78.8%) and 3-year EFS of 58.4%, 95% CI = (43.5%, 78.4%). Table 2 lists all the 3-year EFS and OS and the log-rank comparisons. For first CR patients, 3-year EFS is 74.3%, 95% CI = (62.7%, 88.1%) and 3-year OS 91.6%, 95% CI = (82.4%, 100%). For second CR patients, 3-year EFS is 19.3%, 95% CI = (4.2%, 89.4%) and 3-year OS 66.1%, 95% CI = (36.6%, 100%).

EFS shows significant differences between the first and second cohort of patients ($p = .0029$), whereas OS is not significantly different between both groups ($p = .18$). Figure 2 shows the Kaplan–Meier curves by CR groups showing the significant differences for EFS but not for OS.

TABLE 1 Summary descriptive of all patients in the study by CR cohort

	First CR *n* = 55	Second CR *n* = 18
MYCN status:		
Amplified	12 (21.8%)	5 (27.8%)
Not amplified	43 (78.2%)	13 (72.2%)
Number of previous chemo cycles:		
≤5	7 (12.7%)	5 (27.8%)
>5	48 (87.3%)	13 (72.2%)
Prior ASCT:		
No	45 (81.8%)	6 (33.3%)
Yes	10 (18.2%)	12 (66.7%)
Prior radiotherapy:		
No	35 (63.6%)	2 (11.1%)
Yes	20 (36.4%)	16 (88.9%)
BM MRD:		
No	44 (80.0%)	18 (100.0%)
Yes	11 (20.0%)	0 (0.0%)
Completed treatment:		
No	10 (18.2%)	5 (27.8%)
Yes	45 (81.8%)	13 (72.2%)
Best response after five cycles:		
CR	40 (72.7%)	13 (72.2%)
NE	4 (7.3%)	3 (16.7%)
REL	11 (20.0%)	2 (11.1%)
Age at diagnosis (years)	3.0 (1.2; 6.9)	3.4 (1.2; 8.7)
Age at treatment initiation (years)	3.9 (2.0; 7.8)	5.9 (2.8; 13.9)

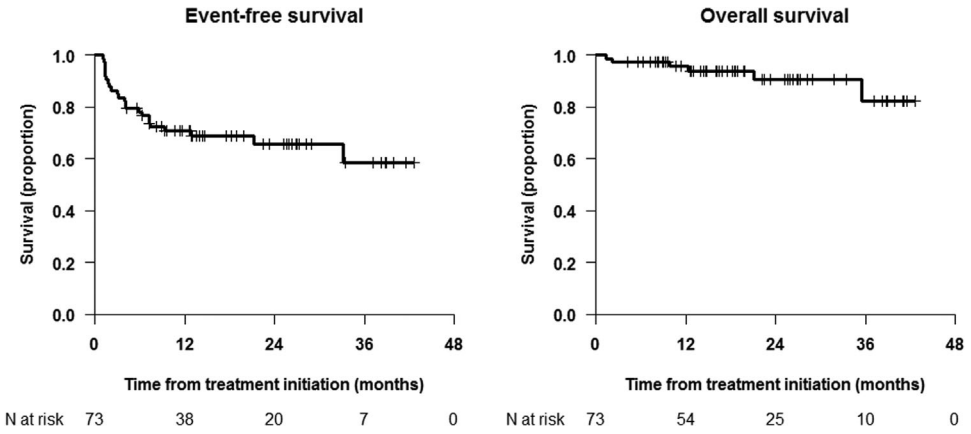

FIGURE 1 Kaplan–Meier survival curves for the whole study population

With a median follow-up of 18.2 months, 13 (24%) out of 55 patients in first CR and 11 (61%) of the 18 patients in second CR relapsed during or after treatment. The pattern of relapse observed show predominance for isolated organ (18/24) relapses including bone (13/24), CNS (2/24; both with prior history of CNS relapse), or soft tissue (3/24). Even among the bone relapses (13/24), five involved only one bone

TABLE 2 Three-year event-free survival (EFS) and overall survival (OS) with comparisons using the log-rank test

	3-year EFS (95% CI)	*p*-Value	3-year OS (95% CI)	*p*-Value
All patients	58.4 (43.5; 78.4)	–	82.4 (66.8; 100.0)	–
CR cohort: First CR	74.3 (62.7; 88.1)	.0029	91.6 (82.4; 100.0)	.18
Second CR	19.3 (4.2; 89.4)		66.1 (36.6; 100.0)	
MYCN status: Amplified	68.4 (48.7; 96.1)	.87	44.1 (10.9; 100.0)	.065
Not amplified	57.0 (40.7; 79.7)		91.6 (82.4; 100.0)	
Number of previous chemo cycles: ≤5	58.2 (33.6; 100.0)	.82	83.3 (58.3; 100.0)	.61
>5	57.1 (38.4; 84.9)		88.2 (78.0; 99.7)	
Prior ASCT: No	64.7 (51.2; 81.6)	.78	77.6 (56.0; 100.0)	.92
Yes	50.3 (26.5; 95.4)		90.2 (78.0; 100.0)	
Prior radiotherapy: No	78.1 (65.8; 92.8)	.062	93.8 (85.8; 100.0)	.64
Yes	45.4 (28.0; 73.7)		79.1 (60.5; 100.0)	
BM MRD: No	58.0 (40.5; 83.0)	.32	82.1 (65.3; 100.0)	.83
Yes	54.5 (31.8; 93.6)		88.9 (70.6; 100.0)	
Age at diagnosis (years): <2.9	65.7 (50.4; 85.5)	.96	80.0 (51.6; 100.0)	.21
≥2.9	51.9 (31.1; 86.5)		84.3 (71.5; 99.3)	
Age at treatment initiation (years): <5.2	73.2 (61.3; 87.5)	.11	80.0 (51.6; 100.0)	.026
≥5.2	38.1 (18.1; 79.9)		75.6 (57.7; 98.9)	

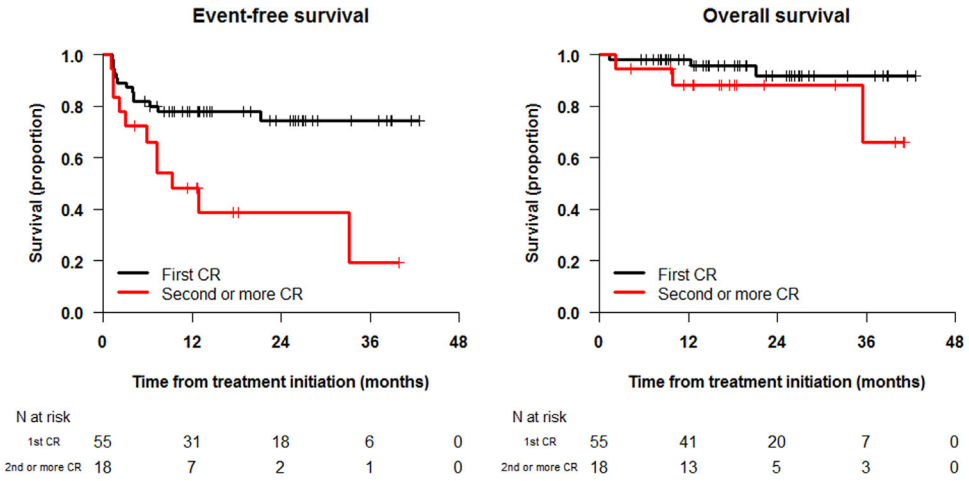

FIGURE 2 Kaplan–Meier survival curves by first/second CR groups showing significant differences for event-free survival (EFS) but not for overall survival (OS)

(Curie score = 1). Three of the 24 relapses included more than one compartment. Interestingly, only one relapse involved the BM (besides bone involvement).

The survival analysis using univariate Cox models including CR cohort, MYCN status, number of chemotherapy cycles administered in the induction period, ASCT and/or radiotherapy before immunotherapy, MRD status (positive -detectable at enrollment), and age at diagnosis or at immunotherapy initiation are shown in Table 3. Only the CR cohort showed significant statistical differences for EFS but not for OS. First CR patients had a significant superior EFS with a hazard ratio of 3.21 ($p = .0047$) compared to second CR group of patients. None of the variables analyzed showed significance for predicting OS. Table 3 lists the hazard ratios for all the variables analyzed.

4 | DISCUSSION

We report on a large cohort of patients with HR-NB in CR after standard induction regimens treated with naxitamab and GM-CSF, but no retinoic acid. Our analysis shows an encouraging survival rate for first

TABLE 3 Univariate analysis using Cox models: hazard ratios and 95% confidence intervals

	EFS		OS	
	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
CR cohort: First CR	Ref.	Ref.	Ref.	Ref.
Second CR	3.21 (1.43; 7.21)	.0047	2.88 (0.58; 14.4)	.20
MYCN status: Amplified	Ref.	Ref.	Ref.	Ref.
Not amplified	1.08 (0.40; 2.91)	.82	0.25 (0.05; 1.23)	.088
Number of previous chemo cycles: ≤5	Ref.	Ref.	Ref.	Ref.
>5	1.13 (0.39; 3.33)	.82	1.77 (0.19; 16.7)	.62
Prior ASCT: No	Ref.	Ref.	Ref.	Ref.
Yes	1.13 (0.48; 2.64)	.78	1.10 (0.20; 6.01)	.92
Prior radiotherapy: No	Ref.	Ref.	Ref.	Ref.
Yes	2.21 (0.94; 5.17)	.069	1.51 (0.26; 8.60)	.64
BM MRD: No	Ref.	Ref.	Ref.	Ref.
Yes	1.65 (0.61; 4.43)	.32	1.27 (0.15; 11.0)	.83
Age at diagnosis (years)	1.08 (0.85; 1.36)	.54	1.05 (0.65; 1.69)	.84
Age at treatment initiation (years)	1.09 (0.95; 1.26)	.21	1.03 (0.75; 1.42)	.87

CR patients with 3-year EFS of 74.3% and OS of 91.6%. With the use of naxitamab and GM-CSF, prognostic significance of markers shown previously to be relevant for HR-NB patients like BM MRD[4,12,20] or MYCN[21] were no longer significant. Also, high-dose chemotherapy and ASCT or radiation therapy prior to immunotherapy did not provide statistically significant advantage for survival. Only prior history of relapse was predictive of further relapse (lower EFS) but not OS. The significant differences between EFS and OS shown for second CR patients reproduce what has been reported in the literature in all studies where anti-GD2 immunotherapy has been evaluated.[8,9,12,20,29,30,33]

Once a uniformly lethal disease, HR-NB is currently potentially curable in highly specialized lefts using myeloablative induction chemotherapy, technologically sophisticated surgery and radiotherapy, and advanced antibody-based anti-GD2 immunotherapy. Unfortunately, this combination of treatments is not available to the majority of children affected by HR-NB. Dissecting the relevance of each modality in the overall contribution of cure is quintessential, if we aim to expand the necessary expertise to treat HR-NB to more lefts in the world. Achieving CR with induction chemotherapy and surgery is the only and most important prognostic feature reproduced in all studies to date.[22–24] Induction chemotherapy and surgery have been fully evaluated and their role in the whole management of HR-NB is solidly demonstrated.[25,26] Furthermore, for patients with MYCN-amplified tumors, achieving first CR is the only real chance to cure as exemplified by the virtually incurable nature of refractory/relapse MYCN-amplified cases in all studies.[27,28] Moreover, the MSKCC experience has shown that MYCN-amplified tumors in first CR have even better survival rates than MYCN nonamplified cases.[21] The role of anti-GD2 immunotherapy has been well demonstrated with large randomized clinical trials.[8–10] The best survival curves shown by large cooperative groups like COG and SIOPEN show EFS rates at 2 and 3 years for first CR patients treated with dinutuximab-based immunotherapy post ASCT 55–65% and OS 85%.[8,10] Most recent update from COG show 5-year EFS of 48% and OS 70%.[9] Our limited single-institution study show similar or superior survival rates at 2 and 3 years for first CR patients treated with naxitamab and GM-CSF without ASCT or cis-RA. This result, in agreement with other experiences,[29,30] questions the relevance of ASCT and cis-RA in the whole management of HR-NB patients in the current era of anti-GD2 immunotherapy.

Preclinical studies[13] showed remarkable differences between naxitamab and other anti-GD2 mAbs. Compared with dinutuximab, naxitamab has 10 times higher affinity for GD2 ganglioside,[31] which translated into augmented efficacy in NB xenograft models. Phase 1 clinical trial findings with naxitamab showed major responses and prolonged progression-free survival as well as an acceptable toxicity profile that allowed outpatient administration,[32] a major difference in quality of life compared to the inpatient administration of the dinutuximab family of MoAbs. The results of the phases 1 and 2 clinical trials run at MSKCC contributed to the US FDA granting, in August 2018, breakthrough therapy designation to naxitamab in combination with GM-CSF for patients with persistent refractory NB limited to B/BM. Subsequently, data from the international phase 2 registration trial (Ymabs 201) prompted the final approval of naxitamab by the US FDA in November 2020.[14] Outside of clinical trial, patients in CR were treated at HSJD with naxitamab and GM-CSF following the same protocol. The toxicity profile of this large cohort of patients has provided increased knowledge on the overall management of naxitamab confirming the safety and feasibility of its outpatient administration. Four patients experienced grade 4 toxicities that impaired the full administration of planned therapy. Among those, two were apneic responses induced by the antibody. One case with grade 4 toxicity was related to the use of opioids manifested as chest rigidity syndrome, a well-known but rare secondary effect of opioids. Finally, one patient presented with stroke between cycles and was taken off therapy,

although causality with naxitamab was not proven. Patient recovered and has not yet shown signs of relapse.

All patients received radiotherapy as consolidation of the primary tumor site, bulky sites at diagnosis, or slow responding sites. In this study, we tested whether radiotherapy administered before or after immunotherapy made any difference in survival or affected the pattern of relapse. Our results do not demonstrate survival or relapse differences between patients receiving radiotherapy before immunotherapy compared to those patients who received radiation at the end of treatment.

A striking observation throughout studies with anti-GD2 antibodies[8,9,12,20,29,30] or bivalent GD2/GD3 vaccine[33] is the significantly discrepant greater impact on OS versus EFS. This is a relevant finding for patients and families, highlighting an unusual case in oncology, that is, relapse is not necessarily a death sentence. The mechanism behind it is still unclear. The isolated relapse pattern may explain, in part, this difference, with relapses post immunotherapy being more amenable to rescue treatments.[12] The potential vaccination effect of an anti-idiotype network released by m3F8 has been hypothesized.[34] Whether an anti-idiotype network is generated with all anti-GD2 antibodies is currently unknown and needs further investigation. Recently published experience of a large cohort of second and further CR HR-NB patients treated with bivalent GD2/GD3 vaccine and oral beta-glucans has shown 5-year EFS of 32% and OS of 71%.[33] In this study, the natural anti-GD2 titers released by the vaccine were associated with outcome. Whether sustained higher anti-GD2 titers explain the limited pattern of relapses and thus a long-term protection effect for patients treated with anti-GD2 strategies needs further confirmation. Another explanation that needs to be tested is whether anti-GD2 immunotherapy has the ability to resensitize tumor cells to cytotoxic therapies and thus provides a better opportunity to achieve subsequent CR for patients relapsing after anti-GD2 immunotherapy. We have recently reported how naxitamab induced NB differentiation in chemo refractory sites of disease.[35] Initial observations in our group suggest that patients treated with naxitamab, upon relapse, show chemo sensitivity to drugs that had previously been refractory.

In conclusion, naxitamab and GM-CSF immunotherapy have resulted in encouraging survival results for HR-NB patients in CR. Prior history of relapse stands as the only predictor of EFS. Fortunately, relapse in this setting is no longer an incurable disease, and therefore special attention should be given in the follow-up of these patients.

ACKNOWLEDGMENTS

Authors acknowledge the Neuroblastoma Immunotherapy Team of nurses and supportive personnel at HSJD. We are grateful to the Band of Parents at Hospital Sant Joan de Déu for supporting the overall research activities of the developmental tumor laboratory, PCCB.

CONFLICT OF INTEREST

Jaume Mora declares consulting fees from Ymabs Therapeutics. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Mora J, Castañeda A, Gorostegui M, et al. Naxitamab combined with granulocyte-macrophage colony-stimulating factor as consolidation for high-risk neuroblastoma patients in complete remission. *Pediatr Blood Cancer*. 2021;e29121. https://doi.org/10.1002/pbc.29121.