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Original Research

Central nervous system relapse in high-risk stage 4 neuroblastoma: The HR-NBL1/SIOPEN trial experience

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KEYWORDS
Neuroblastoma;
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Relapse;
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Anti-GD2

Abstract ***Background:*** There is rising concern on the impact of new strategies, such as high-dose chemotherapy (HDC) and immunotherapy, on the pattern of relapse in high-risk neuroblastoma (HR-NBL). Our aim is to evaluate the incidence and identify risk factors for first recurrence in the central nervous system (CNS) in HR-NBL.
Patients and methods: Data from patients with stage 4V HR-NBL included from February 2002 to June 2015 in the prospective HR-NBL trial of the European International Society of Pediatric Oncology Neuroblastoma Group were analysed. Characteristics at diagnosis, treatment and the pattern of first relapse were studied. CNS imaging at relapse was centrally reviewed.
Results: The 1977 included patients had a median age of 3 years (1 day–20 years); 1163 were boys. Among the 1161 first relapses, 53 were in the CNS, with an overall incidence of 2.7%, representing 6.2% of all metastatic relapses. One- and three-year post-relapse overall survival was 25 ± 6% and 8 ± 4%, respectively. Higher risk of CNS recurrence was associated with female sex (hazard ratio [HR] = 2.0 [95% confidence interval {CI}: 1.1–3.5]; $P = 0.016$), *MYCN*-amplification (HR = 2.4 [95% CI: 1.2–4.4]; $P = 0.008$), liver (HR = 2.5 [95% CI: 1.2–5.1]; $P = 0.01$) or >1 metastatic compartment involvement (HR = 7.1 [95% CI: 1.0–48.4]; $P = 0.047$) at diagnosis. Neither HDC nor immunotherapy was associated with higher risk of CNS recurrence. Stable incidence of CNS relapse was reported over time.
Conclusions: The risk of CNS recurrence is linked to both patient and disease characteristics, with neither impact of HDC nor immunotherapy. These findings support the current treatment strategy and do not justify a CNS prophylactic treatment.
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1. Introduction

High-risk neuroblastoma (HR-NBL) represents a major clinical challenge in pediatric oncology. The introduction of high-dose chemotherapy (HDC) followed by autologous stem cell rescue (ASCR) has increased survival rates [1–3]. However, long-term survival is still poor, and around half of the patients relapse. Immunotherapy has further improved outcomes, but the long-term impact still has to be evaluated [4–6].

There is a rising concern on the impact of new strategies (i.e. HDC regimens and immunotherapy) on the pattern of relapse, especially taking into account that anti-disialoganglioside (GD2) antibodies do not penetrate the blood–brain barrier, potentially allowing the central nervous system (CNS) to emerge as a sanctuary site leading to a higher proportion of CNS recurrences [7,8]. Few data have been reported in the literature on the incidence of CNS relapse in this population [7–10]. The precise analysis of CNS recurrence is of major interest, as it may impact the design of future HR-NBL strategies.

The European Society of Paediatric Oncology Neuroblastoma Group initiated a multicentre, international, randomised phase III trial (HR-NBL1/SIOPEN) that recruited patients from 2002. This prospectively collected cohort provides a unique opportunity to identify the incidence and risk factors of CNS recurrence at first relapse in a well-characterised population. Moreover, the analysis of this cohort permits the evaluation of the impact of different HDC regimens and the administration of immunotherapy on the risk of CNS involvement at recurrence.

2. Patients and methods

2.1. Patients, disease and treatment features

Patients enrolled in the HR-NBL1/SIOPEN trial (NCT00030719) from February 2002 to June 2015 with newly diagnosed stage 4 HR-NBL, older than 12 months regardless of *MYCN* status or younger than 12 months with *MYCN*-amplified tumours, were included in this analysis [11,12].

They received Rapid COJEC induction chemotherapy with or without topotecan–vincristine–doxorubicin (TVD), continuing to HDC followed by ASCR if they reached the 'R1' criteria [13]: at least a 50% reduction in skeletal iodine-123-meta-iodobenzylguanidine (MIBG) positivity and no more than three residual positive spots, as well as

complete bone marrow remission. From 2002 to 2010, patients were randomised to receive HDC with either busulfan–melphalan (Bu–Mel) or carboplatin/etoposide/melphalan (CEM). After 2010 Bu–Mel became the SIOPEN HDC standard of care following the outcome of the randomised trial showing the significant benefit of Bu–Mel over CEM in this cohort of patients [13]. Local treatment was to aim for complete primary tumour resection, followed by radiotherapy (21 Gy) to the tumor bed. Maintenance treatment was 13-cis retinoic acid alone until 2010, after which it was combined with immunotherapy (dinutuximab beta ± interleukin-2).

The trial was approved by national regulatory authorities and by national and institutional ethical committees. Parents or guardians of patients younger than 18 years and adult patients provided written informed consent before enrolment.

Data regarding clinical presentation (age, sex, stage, primary and metastatic sites), *MYCN* status, treatment type (additional TVD, HDC regimen, maintenance treatment), disease response at the end of induction, before maintenance and at the end of treatment, follow-up and first relapse were prospectively collected in the HR-NBL1/SIOPEN database. Only first recurrences were considered for this analysis. Cranial imaging was not systematically requested in patients without MIBG-avid skull metastases in the HR-NBL1/SIOPEN trial. CNS relapse was defined as the appearance of a new leptomeningeal or parenchymal lesion, excluding metastases originating in the bone of the skull.

2.2. Central review of imaging

A secure web-based system, featuring automated de-identification of DICOM images, was developed and provided by the AIT Austrian Institute of Technology within the frame of SIOPEN-R-NET, to perform retrospective central imaging review. Brain computed tomography (CT), brain/spine magnetic resonance imaging (MRI) and MIBG scans were requested for all patients with identified CNS recurrence at first relapse. Image gathering and uploading was organised in six centres and, subsequently, centrally reviewed by a pediatric radiologist (C.S.) and a nuclear medicine expert (R.C.).

2.3. Statistical methods

Categorical variables were described with the numerical count (percentage) of each category. Continuous variables were described as median, minimum and maximum. Event-free survival (EFS) and overall survival (OS) [14] were estimated using the Kaplan–Meier method and compared by the log-rank test. For EFS, relapses, progressions, death from any cause and secondary malignancies were considered as an event. For OS, death from any cause was considered as an event. Patients without an event were censored at the date of the last follow-up. The interval was from time of diagnosis and, for post-relapse survival, from the time of the first relapse/progression. Cumulative incidences for CNS relapses were estimated taking into account the competing risk of non-CNS relapse/progression, death from any cause and secondary malignancies [14]. Gray's method was used for the statistical comparison of cumulative incidence, and multivariable analysis was performed by the model of Fine and Gray [15]. For the evaluation of HDC and maintenance treatment, the interval starts with HDC and maintenance treatment, respectively. A separate Fine and Gray model adjusted for sex, age, *MYCN*, liver metastases and number of metastatic components was performed to investigate the impact of HDC on CNS-relapses. For the evaluation of maintenance treatment, the model was additionally adjusted for HDC. $P < 0.05$ was considered as statistically significant. Data were analysed using SAS 9.4.

3. Results

In the HR-NBL1/SIOPEN trial, 1977 patients with stage 4 HR-NBL were included in 170 centres from 19 countries. Of these, 1163 were boys. The median age at diagnosis was 3.0 years (range: 1 day–20 years). Among the whole cohort, 1161/1977 (59%) patients presented with at least one relapse/progression before January 2016, with a median follow-up of 5.2 years (interquartile range: 2.1–6.5 years). Of these, 855 had a metastatic relapse (disseminated or combined), and 63 patients were reported as presenting with CNS involvement at first recurrence. Central review confirmed a CNS relapse in 54/59 evaluable patients, which corresponds to 92% of confirmed CNS relapses (95% confidence interval [CI]: 82–96%). One patient with a confirmed CNS relapse, but not as first relapse, was not included in the CNS cohort. The five patients for whom the CNS relapse was not confirmed had skull bone relapses with intracranial extension, with neither parenchymal nor leptomeningeal involvement.

A final cohort of 53 confirmed CNS relapses as first recurrence was considered in the CNS analysis population (Figure 1; Supplementary Table 1). Among patients with stage 4 HR-NBL, the incidence of CNS relapse represented 2.7% of the whole cohort and 6.2% of the metastatic relapses.

3.1. Clinical and radiological features of CNS relapses

The median time to CNS recurrence from diagnosis was 1.0 year (range: 0.2–2.5 years), compared with 1.2 years (range: 0.02–8.3 years) for relapses at other sites ($p = 0.05$). Most of the CNS relapses (90%) were diagnosed based on neurological symptoms (intracranial

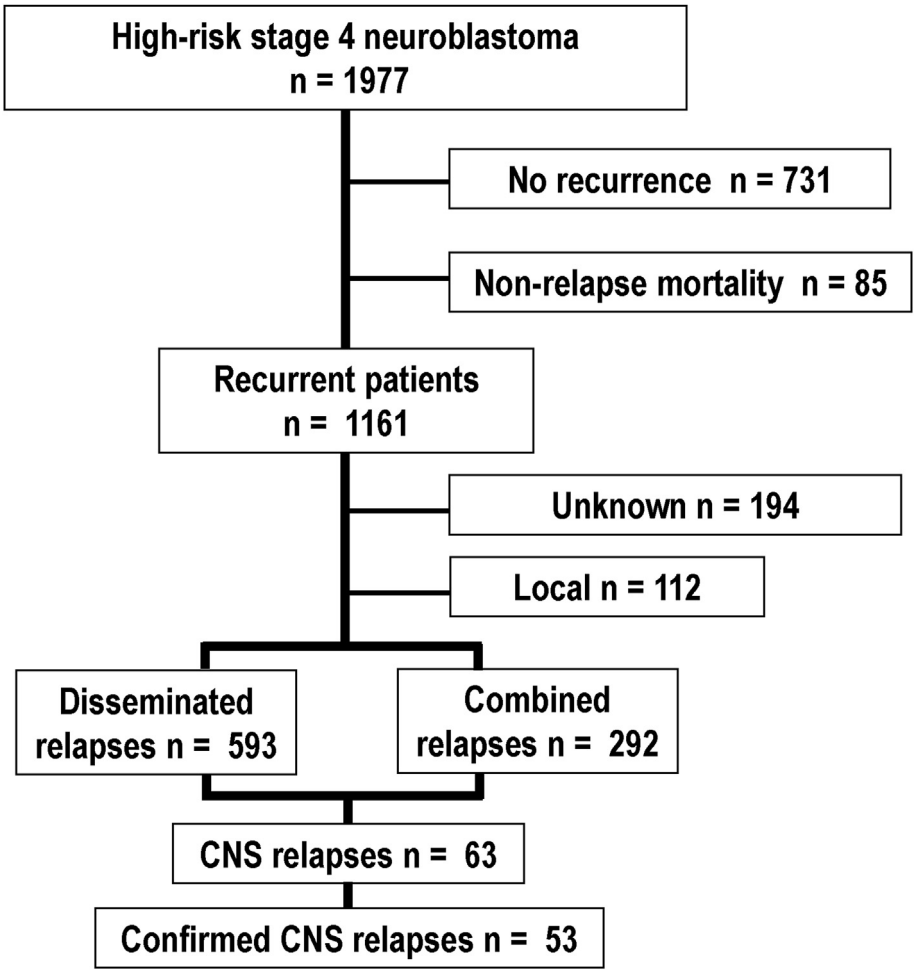

Fig. 1. The HR-NBL1/SIOPEN patients' recurrences flowchart. CNS: central nervous system.

hypertension, seizures, etc.) and occurred mainly before the end of treatment (39/53; 74%).

Brain MRI/CT scans were performed at diagnosis in 14/53 patients; only two of these presented with CNS involvement at primary diagnosis. A complete disease evaluation at relapse was performed in 40/53 patients, revealing isolated CNS relapse in 18/40 patients (45%) and combined relapse, mainly bone involvement, in 22/40 patients (55%). CNS lesions were mainly supratentorial, presenting as a unique lesion in half of the patients (Supplementary Figure 1). Leptomeningeal disease was found in 7/27 evaluable patients. The main reason for lack of neuroaxis imaging was rapidly disease progression with clinical deterioration. The MIBG scan at the time of relapse was available for a central review in 10/53 patients, and CNS metastases could be identified on MIBG scan in 6/10 patients.

3.2. Outcome of patients with CNS relapse at first recurrence

Eighteen of 53 patients did not receive any treatment at relapse because of rapidly disease progression (Figure 2). Twenty-seven patients were treated with chemotherapy, mainly temozolomide-containing regimens (22/27). Thirteen patients underwent surgery of the CNS lesion(s). Radiotherapy was performed in 18 patients, with cranio-spinal irradiation in 10 of them.

Post-relapse one-year and three-year OS was 25 ± 6% and 7 ± 4%, respectively. Median survival time after the diagnosis of the CNS recurrence was 4 months (range: 0–82 months). Although the short-term survival of patients with CNS relapse after the end of treatment was longer than for those with earlier CNS relapse (post-relapse one-year OS: 45 ± 11% versus 12 ± 6%, $p = 0.026$), long-term survival rates were similarly poor (post-relapse three-year OS: 10 ± 7% versus 6 ± 4%) (Supplementary Figure 2). Patients with isolated CNS recurrence had a better outcome ($p = 0.007$) than those with a combined relapse (Figure 3A). Post-relapse one-year OS was worse for children with CNS recurrence than patients with relapses to other sites ($p < 0.002$), although long-term survival was as poor for both groups (Figure 3B). Among those patients for whom at least one treatment modality was applied (n = 31), three patients were alive with a follow-up of 4.7, 4.9 and 10.1

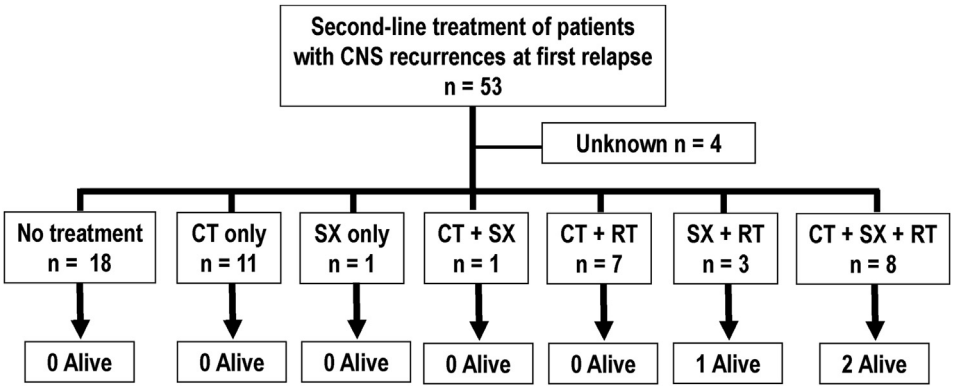

Fig. 2. The flowchart of second-line treatment and outcome of patients with CNS recurrences at first relapse. CNS: central nervous system, CT: chemotherapy, SX: surgery, RT: radiotherapy.

years (Supplementary Figure 3). Of note, all three patients presented with a single CNS lesion without any further metastatic involvement and were treated with complete surgical excision, cranio-spinal radiotherapy, and all but one received second-line chemotherapy with a temozolomide-containing regimen.

3.3. Risk factors of CNS relapse in stage 4 HR-NBL

In the univariate analysis, *MYCN* amplification (4 ± 1% versus 2 ± 0%, p = 0.005), liver involvement (8 ± 2% versus 2 ± 0%, p < 0.001), and >1 metastatic system/compartment (3 ± 0% versus 0 ± 0%, p = 0.048) at diagnosis (Table 1) were significantly associated with a higher incidence of CNS relapse. No significant impact on the incidence of CNS relapse was shown in accordance with the HDC regimen (Bu–Mel, n = 819 versus CEM, n = 253), with a CNS incidence of 3 ± 1% versus 3 ± 1% (p = 0.831), respectively (Table 1; Supplementary Figure 4A). The administration of dinutuximab beta (n = 350) did not significantly influence the risk of CNS recurrence when compared with retinoic acid only (3 ± 1% versus 3 ± 1%, p = 0.983) (Supplementary Figure 4B), and the administration of IL-2 had no impact on the incidence of CNS recurrence (p = 0.88) (data not shown). The incidence of CNS recurrence did not increase in patients registered before and after 2009 (3 ± 1% versus 3 ± 1%, respectively; p = 0.486), being 2010 the year when dinutuximab beta was introduced into the HR-NBL1 trial (Supplementary Figure 4C).

In the multivariate analysis, female sex (sub-distribution hazard ratio evaluating hazards for CNS relapses taking into account the competing events [sHR]: 2.0 [1.1–3.5]; p = 0.016), *MYCN* status (sHR: 2.4 [1.2–4.4]; p = 0.008), hepatic (sHR: 2.5 [1.2–5.1]. p = 0.013) and >1 metastatic system/compartment involvement (sHR: 7.1 [1.0–48.4]; p = 0.047) were independent significant risk factors (Table 1) at diagnosis. On the other hand, adjusted for sex, age, liver metastases and number of metastatic compartments, no impact of the HDC regimen (sHR: 0.9 [0.4–2.1]; p = 0.787) was found. The same was true when the impact of immunotherapy adjusted for these prognostic

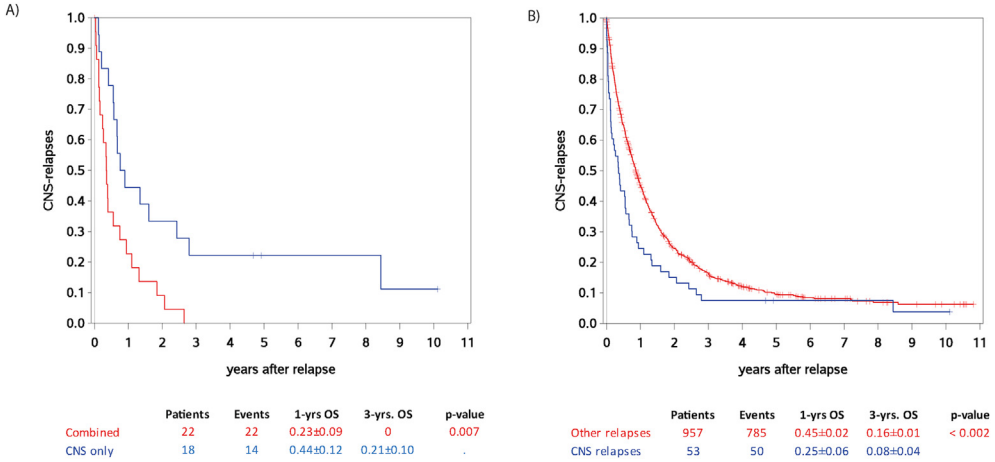

Fig. 3. Post-relapse overall survival (OS) of A) patients with central nervous system (CNS) recurrence, according to the disease extension at first relapse B) patients with stage IV high-risk neuroblastoma in accordance with the site of relapse.

Table 1
Comparison of patients and disease's characteristics at diagnosis as well as treatment features for patients with stage 4 neuroblastoma with and without CNS relapse (univariate and multivariate analysis).

		Patients	Univariate analysis					p-value	Multivariate analysis	
			CNS relapses			Event-free survival			CNS relapses	
			Events	5-year CI	p-value	Events	5-year EFS		sHR (95% CI)	p-value
A) Risk factors at diagnosis										
Sex	Male	1163	25	0.02 ± 0.00	0.077	729	0.32 ± 0.02	0.293	1	0.016
	Female	814	28	0.04 ± 0.01		517	0.30 ± 0.02		2.0 (1.1–3.5)	
Age	<1 year	98	6	0.07 ± 0.03	0.111	47	0.45 ± 0.06	0.011	1	
	1–1.5 yrs	191	5	0.03 ± 0.01		100	0.44 ± 0.04		0.6 (0.1–2.1)	0.377
	1.5–5 yrs	1277	34	0.03 ± 0.00		801	0.32 ± 0.01		0.7 (0.3–1.9)	0.501
	>5 yrs	411	8	0.02 ± 0.01		298	0.20 ± 0.02		0.67 (0.2–2.4)	0.539
***MYCN* status**	MNA−	1090	20	0.02 ± 0.00	0.005	698	0.29 ± 0.02	0.265	1	
	MNA+	738	30	0.04 ± 0.01		459	0.33 ± 0.02		2.4 (1.2–4.4)	0.008
Metastatic sites									–	
BM	−	376	7	0.02 ± 0.01	0.231	190	0.46 ± 0.03	<0.001		
	+	1497	45	0.03 ± 0.00		1002	0.27 ± 0.01			
Skeleton	−	311	8	0.03 ± 0.01	0.767	172	0.40 ± 0.03	0.016	–	
	+	1545	45	0.03 ± 0.00		1000	0.30 ± 0.01			
Liver	−	1599	37	0.02 ± 0.00	<0.001	102	0.31 ± 0.01	0.042	1	
	+	225	16	0.08 ± 0.02		148	0.28 ± 0.03		2.5 (1.2–5.1)	0.013
Pulmonary	−	1686	47	0.03 ± 0.00	0.895	1071	0.31 ± 0.01	<0.001	–	
	+	134	4	0.03 ± 0.02		226	0.22 ± 0.04			
Meta. Comp.	1	222	1	0.00 ± 0.00	0.048	330	0.49 ± 0.04	<0.001	1	
	>1	1546	50	0.03 ± 0.00		1016	0.29 ± 0.01		7.1 (1.0–48.4)	0.047
Time period	<2009	1015	26	0.03 ± 0.01	0.486	735	0.28 ± 0.01	0.003	–	
	≥2009	962	27	0.03 ± 0.01		511	0.34 ± 0.02			
B) Treatments										
High-dose therapy	BUMEL	819	24	0.03 ± 0.01	0.831	432	0.42 ± 0.02	<0.001	0.9 (0.4–2.1)[a]	0.787
	CEM	253	7	0.03 ± 0.01		181	0.30 ± 0.03			
Maintenance	Retinoic acid	522	14	0.03 ± 0.01	0.983	322	0.38 ± 0.02	<0.001	1.1 (0.4–2.8)[b]	0.817
	Immunotherapy	350	9	0.03 ± 0.01		132	0.54 ± 0.03			

CEM: carboplatin/etoposide/melphalan; CI: confidence interval; CNS: central nervous system; BM: bone marrow; Meta. Comp: number of metastatic components; CI: confidence interval; sHR: subdistribution hazard ratio evaluating hazards for CNS relapses taking into account the competing events; EFS: event-free survival.
[a] Adjusted for sex, age, *MYCN*, liver metastases and number of metastatic components.
[b] Adjusted for sex, age, *MYCN*, liver metastases, number of metastatic components and HDC.

factors and HDC (sHR: 1.1 [0.4–2.8]; p = 0.817) was evaluated.

4. Discussion

Few and discordant data have been reported so far in the literature on the incidence of CNS relapse in patients with HR-NBL, and some of them suggested an increased rate of CNS involvement over time [7–10]. The Children's Oncology Group (COG) confirmed CNS relapses at first recurrence in 8 (2%) of 434 patients older than 12 months with stage 4 neuroblastoma that were registered in the COG3891 protocol from 1991 to 1996 [9]. In a French retrospective analysis of 434 children with stage 4 neuroblastoma diagnosed between 1985 and 2000, disease progression occurred in 225 patients, including 23 patients (5%) with radiologically confirmed metastases at the CNS at first recurrence [10]. Among the 127 patients with stage 4 neuroblastoma diagnosed at Memorial Sloan Kettering (MSK) between 1980 and 1999, eight patients (6%) developed confirmed CNS relapses. In this cohort, the incidence of CNS metastases seemed to be more frequent in patients previously treated with immunotherapy and no HDC (7/67), in comparison with patients that received HDC and no immunotherapy (1/60) [7]. According to the German experience, CNS relapses were reported in 49 (11%) of 451 patients with HR-NBL (stage 4, stage 3 MYCN-amplified tumours) treated with HDC as part of the first-line treatment from 1990 to 2007 [8]. A central review of imaging was not reported. Although some of these patients had previously received anti-GD2 as part of the maintenance therapy, no separate analysis of the two populations treated with or without immunotherapy was done.

In our cohort, the incidence of CNS relapse represented 2.7% of the total number of relapses and 6.2% of the metastatic relapses. The reported incidence of CNS recurrences at first relapse is similar to the COG experience [9] but lower than in other reports [7,8,10]. This may be partially explained by the smaller patient cohorts of previous studies and by the lack of a central

review of imaging. However, the incidence of CNS recurrences at first relapse in our cohort may also be underestimated. It is important to highlight that cranial imaging was not requested in patients without MIBG-avid skull metastases in the HR-NBL1/SIOPEN trial; therefore, it may have been selectively performed in symptomatic patients only. Nevertheless and most importantly, our results do not confirm a trend towards a higher proportion of CNS recurrences over time, as suggested in previous reports as a result of better control of other metastatic sites and lack of anti-GD2 antibodies blood–brain barrier penetrance [7,8]. Indeed, neither the HDC regimen nor the use of immunotherapy was associated with a higher risk of CNS involvement at first relapse. On the contrary, patient and disease features at diagnosis, such as female sex, *MYCN* amplification, hepatic and >1 metastatic system/compartment involvement, were identified as significant risk factors for CNS relapse. Only two of the previously published studies performed an analysis of prognostic factors for CNS relapse and univariate analyses showed that LDH and lumbar puncture at diagnosis [7], or age, lumbar puncture at diagnosis and *MYCN*-amplification [10] were risk factors for CNS recurrence. Concerning lumbar puncture, this is not recommended in the HR-NBL1/SIOPEN trial; therefore this information is not captured in the database and could not be analysed. Nevertheless, as lumbar puncture at diagnosis might be performed in patients with neurological symptoms, it seems a likely source of bias rather than a real risk factor of CNS involvement.

Post-relapse OS of patients with CNS recurrence is extremely poor (post-relapse first-year and three-year of OS of 25 ± 6% and 7 ± 4%), although long-term survival was equally poor in relapses to other sites. Nevertheless, in our cohort 3/17 patients with isolated CNS relapses who were treated with complete surgery, cranio-spinal radiotherapy and chemotherapy, mainly temozolomide-containing regimens, are long-term survivors.

In the St. Jude Children's Research Hospital experience, four of 10 children with CNS relapse treated between 1978 and 1989 received cranio-spinal radiotherapy (±surgery and chemotherapy), and two of them were alive and free of disease at 50 and 62 months after CNS relapse [16]. In another retrospective analysis of 29 patients with CNS relapses treated in the MSK between 1987 and 2007, none of the patients treated before 2003 with focal radiotherapy survived, although 12 of 16 patients treated with surgical resection, cranio-spinal irradiation with irinotecan as radiosensitizer, followed by irinotecan–temozolomide ± carboplatin and intrathecal radio-iodinated monoclonal antibodies (3F8 or 8H9), were alive without CNS disease with a median of 28 months of follow-up [7,17]. This higher survival may be at least partially explained by a selection bias, as patients with CNS relapses receiving multimodal treatment are a population with better prognosis as shown in our cohort.

In conclusion, this study provides data on the incidence, risk factors and outcome of CNS recurrence at first relapse in a large, prospective and unselected cohort of patients with HR-NBL. Our results do not show a trend toward an increasing risk of CNS recurrence over time, nor do they display a significant impact of the HDC regimen or immunotherapy, thus not justifying a change in the current treatment strategy. Moreover, the low incidence of CNS recurrence in our population does not seem to justify prophylactic treatment in future trials either. Finally, it is important to underline that long-term survival can still be achieved, mainly in patients with isolated CNS relapse. It will be of major importance to identify future strategies that might help to achieve an earlier diagnosis of non-symptomatic CNS involvement to allow adequate multimodal treatment.

Author contribution statement

Pablo Berlanga: Conceptualization, Methodology, Validation, Investigation, Data Curation, Visualization, Writing - Original Draft, Writing - Review & Editing, Project administration; **Claudia Pasqualini**: Conceptualization, Validation, Investigation, Data Curation, Visualization, Writing - Original Draft, Writing - Review & Editing, Project administration; **Ulrike Pötschger**: Methodology, Formal analysis, Validation, Data Curation, Visualization, Writing - Original Draft, Writing - Review & Editing; **Cinta Sangüesa**: Investigation, Resources, Writing - Review & Editing; **Maria Rita Castellani**: Investigation, Resources, Writing - Review & Editing; **Adela Cañete**: Resources, Writing - Review & Editing; **Roberto Luksch**: Resources, Writing - Review & Editing; **Martin Elliot**: Resources, Writing - Review & Editing; **Günter Schreier**: Software, Resources, Writing - Review & Editing; **Martin Kropf**: Software, Resources, Writing - Review & Editing; **Daniel Morgenstern**: Resources, Writing - Review & Editing; **Vassilios Papadakis**: Resources, Writing - Review & Editing; **Shifra Ash**: Resources, Writing - Review & Editing; **Ellen Ruud**: Resources, Writing - Review & Editing; **Penelope Brock**: Resources, Writing - Review & Editing; **Aleksandra Wieczorek**: Resources, Writing - Review & Editing; **Per Kogner**: Resources, Writing - Review & Editing; **Toby Trahair**: Resources, Writing - Review & Editing; **Peter Ambros**: Resources, Writing - Review & Editing; **Tom Boterberg**: Resources, Writing - Review & Editing; **Victoria Castel**: Conceptualization, Resources, Writing - Review & Editing; **Dominique Valteau-Couanet**: Conceptualization, Resources, Supervision, Writing - Original Draft, Writing - Review & Editing; **Ruth Ladenstein**: Conceptualization, Resources, Supervision, Writing - Original Draft, Writing - Review & Editing, Funding Acquisition

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.10.020.

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