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Original Research

Predictors of differential response to induction therapy in high-risk neuroblastoma: A report from the Children's Oncology Group (COG)

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Abstract ***Background:*** Induction chemotherapy plays an important role in the management of patients with high-risk neuroblastoma. Predictors of response to induction therapy are largely lacking. We sought to describe clinical and biological features associated with induction response.

Methods: Patients from four consecutive COG high-risk trials were included. Response was evaluated by the 1993 International Neuroblastoma Response Criteria. The primary endpoint was end-induction partial response (PR) or better. Univariate analyses were performed to compare response as a function of clinical or biologic predictors. A multivariate logistic regression model using significant predictors from univariate analyses was constructed to model PR or better.

Results: The analytic cohort included 1242 patients. End-induction response ≥PR was significantly associated with higher event-free and overall survival. Baseline factors associated with

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≥PR included age <18 months (87.4% with ≥PR vs. 78.7% if older; $p = 0.0103$), International Neuroblastoma Staging System non-stage 4 (89.0% vs. 78.4% if stage 4; $p = 0.0016$), *MYCN* amplification (85.5% vs. 77.1% if non-amplified; $p = 0.0006$), 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no LOH; $p = 0.0085$), no 11q LOH (84.8% vs. 70.9% if 11q LOH; $p = 0.0004$) and high mitosis-karyorrhexis index (MKI; 84.5% vs. 77.5% if low-intermediate MKI; $p = 0.0098$). On multivariable analysis (n = 407), the absence of 11q LOH was the only factor that remained significantly associated with ≥PR (odds ratio: 1.962 vs. 11q LOH; 95% confidence interval 1.104–3.487; $p = 0.0216$).

Conclusions: Improved end-induction response in high-risk neuroblastoma is associated with longer survival. Patients with 11q LOH are less likely to respond to induction therapies and should be prioritised for novel approaches in future trials.

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1. Introduction

Neuroblastoma is a malignancy of the sympathetic nervous system and the most common malignancy in infancy. Neuroblastoma is notable for its marked clinical heterogeneity ranging from spontaneous regression without intervention to highly fatal chemoresistant disease [1]. Several clinical and tumour biologic factors identify patients at low, intermediate or high risk of relapse and are used to assign upfront therapy [2]. Outcomes for patients with high-risk neuroblastoma (representing approximately 40% of new neuroblastoma cases) are historically poor, with 5-year disease-free survival less than 50% [3–5]. The addition of myeloablative chemotherapy followed by autologous stem cell transplant (ASCT) rescue after induction therapy improved surgical and radiotherapy techniques, and the use of both a differentiating agent (cis-retinoic acid) and a chimeric anti-GD2 antibody after transplantation has led to incremental improvements in the disease-free survival [6]. Despite multimodal therapy, durable remission rates remain low, with 10–15% of patients progressing during induction therapy and another 40% progressing after an initial response to induction [4,5]. The ability to identify both clinical and biologic prognostic markers of response early in a patient's clinical course may significantly affect subsequent therapy, identifying individuals who may benefit from augmented or alternative therapy.

Induction therapy plays a critical role in the management of patients with high-risk neuroblastoma. The goal of induction therapy is to obtain maximal reduction in tumour burden before planned consolidation therapy with high-dose chemotherapy and stem cell rescue [7]. Induction typically consists of intensive multiagent chemotherapy and surgical resection of the primary tumour. Prior studies have demonstrated that favourable response to induction therapy is associated with favourable event-free survival (EFS) [8–10]. However, predictors of response to induction therapy itself are surprisingly lacking. Increased dose intensity appears to be associated with higher response rate [11,12], although little is known about the impact of treatment delays and dose reductions during induction in patients intended to receive similar chemotherapy regimens. Receipt of 5 vs. 6 cycles of induction chemotherapy does not appear to impact rate of response to induction [13]. In a recent Children's Oncology Group (COG) analysis of *MYCN* copy number, patients with *MYCN* amplification had a 25.1% complete induction response rate compared with 12.4% for patients with *MYCN* wild-type tumours [14]. Whether other clinical or biological features impact likelihood of response to induction chemotherapy is largely unknown.

The COG has conducted a series of four clinical trials since 2001 which used intensive induction chemotherapy for 5–6 cycles [5,13,15,16]. During this same time period, response was graded uniformly using the 1993 version of the International Neuroblastoma Response Criteria (INRC), which uses a combination of radiographic, pathologic and biochemical parameters to determine overall response to treatment [17]. These trials enrolled a total of 1315 eligible high-risk patients, providing a robust data set in which to perform a comprehensive evaluation of potential predictors of favourable and unfavourable response to induction therapy. In the present report, we used this data set to describe clinical and biological features associated with response to induction therapy using the following categories of response: partial response (PR) or better; complete response (CR) or progressive disease (PD). For patients who had an early response assessment (before the end of induction), we also sought to describe clinical and biological features that are associated with early response during induction therapy.

2. Materials and methods

2.1. Patients

Patients from the following trials were considered for inclusion in the study: A3973 [5], ANBL02P1 [15], ANBL0532 [16] and ANBL12P1 [13]. Patients with at

least one disease evaluation during induction after initiating protocol therapy and those with early PD who were missing end-induction response were eligible for inclusion in the analytic cohort. Response was evaluated at two time points during induction: early response assessment and end-induction response assessment. The early response assessment was captured after 2 induction cycles for A3973, ANBL02P1 and ANBL0532 and 4 cycles for ANBL12P1. The end-induction response assessment was captured after 5 cycles for ANBL12P1 and after 6 cycles for the other studies. Patients who developed PD after 2 cycles of therapy on studies ANBL02P1 and ANBL0532 were eligible to remain on study to complete the remainder of induction therapy as long as they did not continue to progress. Patients on ANBL12P1 with PD after 4 cycles could either end protocol therapy or remain on study at the discretion of the treating physician. Patients who developed PD on A3973 at an early time point were taken off protocol therapy. Patients with early PD who were missing end-induction response were coded as having PD at end induction.

2.2. Variables

End-induction overall response (≥PR or <PR) was the primary end-point, whereas end-induction CR or PD were secondary response end-point. Similarly, early PR or early PD were additional secondary response end-points. All included trials used the 1993 INRC to evaluate response to induction therapy, with primary site response based on response achieved from the combination of surgery and chemotherapy (Supplemental Table 1) [17].

Potential baseline predictor variables included age at diagnosis, sex, race, ethnicity, International Neuroblastoma Staging System (INSS) stage [17], primary site, metastatic site, International Neuroblastoma Pathology Criteria (INPC) histology [18], mitosis-karyorrhexis index (MKI), tumour grade, *MYCN* status (amplified versus non-amplified), *ALK* status (wild type vs mutant/amplified), chromosome 1p loss of heterozygosity (LOH), chromosome 11q LOH, tumour ploidy and metaiodobenzylguanidine (MIBG) avidity (only available for A3973 and ANBL12P1). Age at diagnosis was evaluated using two binary variables: both an 18-month cut-off (optimised as prognostic of EFS) [19] and a 5-year cut-off (selected for descriptive purposes). LOH data were not collected on ANBL02P1. Potential predictor variables collected after initiation of chemotherapy included response assessed at an early time point, chemotherapy dose modifications (only available for A3973 and ANBL02P1) and treatment delays (analysed as duration of induction divided by total number of induction cycles). All induction cycles were intended to be 21 days in length. For each study, a treatment delay was defined as taking longer than the following calculation: 21 days times the number of induction cycles, plus 7 days per cycle completed, 14 days for surgery and 12 days for transplant preparation if all induction cycles were completed (COG policy allows minor unavoidable departures of up to 72 h from protocol directed therapy and up to 1 week for surgery for valid clinical, patient, and logistical issues). Not all potential predictor variables were collected on all four clinical trials. As such, some variables have missing data for all patients enrolled to a trial in which the variable was not included on the trial case report forms.

2.3. Statistical considerations

Kaplan–Meier methods and log-rank tests were used to compare EFS and overall survival (OS) according to groups defined by end-induction response category. EFS was calculated as time from initial diagnosis to the first episode of disease relapse or progression, second malignancy or death, with patients without event censored at the last follow-up. OS was calculated as time from initial diagnosis to death, with surviving patients censored at the last follow-up.

A series of univariate analyses (Fisher's exact or chi-squared tests, depending on the sample size with available data) were performed to compare response (PR or better) as a function of each predictor variable. These analyses were repeated to compare CR and PD as a function of each predictor variable. Early response assessment after 2–4 cycles of induction was a predictor variable, but we also assessed predictors of early response and early disease progression. For each predictor variable, the Holm–Bonferroni method was applied to p-values across the 3 different response dichotomisations (PR or better, CR and PD) to correct for multiple testing [20] using different cut-offs of the same response variable, using a family-wise error rate of 0.05.

A series of multivariable logistic regression models using the predictors that were statistically significant from the univariate analyses were constructed to model PR or better and separately to model CR or < CR. The goal of these models was to assess whether univariate significant predictors remained significant after controlling for other univariate significant predictors. For the model of CR, multivariable logistic regression models were run with and without MIBG avidity as a predictor because MIBG avidity data were available from only two studies. Similarly, models were constructed with and without 1p and 11q status due to >50% missing data in the overall cohort. For all models, the odds ratios (ORs) compared the more favourable category with the less favourable category (reference level) for each factor. P-values from multivariable models were not adjusted for multiple comparisons.

3. Results

3.1. Patient characteristics

Of the 1315 high-risk patients, 1280 patients (A3973: 470; ANBL02P1: 31; ANBL0532: 638; ANBL12P1: 141) met eligibility criteria of this study, with at least one disease evaluation or early PD after initiating protocol therapy (Fig. 1). Thirty-five patients did not have a reported disease evaluation (Fig. 1) and were excluded. Nine hundred ninety-six (996) patients (A3973: 300; ANBL02P1: 30; ANBL0532: 545; ANBL12P1: 121) had early response evaluations, and 1242 patients (A3973: 457; ANBL02P1: 30; ANBL0532: 626; ANBL12P1: 129) had end-induction response evaluations.

Clinical and biological features are shown in Table 1 and are as expected for this population. Data on tumour biological features other than *MYCN* status or ploidy (e.g. *ALK* status and segmental LOH at 1p or 11q) were missing in more than 50% of the data set as these data were not collected on all four included trials. Among patients with available data on treatment delays or modifications, 13.3% met the definition of induction treatment delay and 11.7% had a reported chemotherapy dose modification during induction.

3.2. End-induction response is associated with EFS and OS

We first sought to determine if end-induction response was associated with EFS and OS, as has been reported in prior analyses [10,21]. In the full cohort of 1242 patients, 79.8% of patients had PR or better at end induction. End-induction CR was reported in 20.8% of patients. Patients with either ≥ PR or CR at end induction had significantly superior EFS (Fig. 2A and B) and OS (Fig. 2C and D) compared with patients with <PR or <CR ($p < 0.0001$ for all comparisons).

3.3. Univariate predictors of PR or better at end induction

The end-induction PR rate differed significantly by subgroups (Table 1). Among factors potentially known at initial presentation, the following variables were significantly associated with a PR or better, even after controlling for multiple testing: age <18 months (87.4% with PR or better vs. 78.7% if older; $p = 0.0103$), age <5 years (82.0% vs. 70.6% if older; $p < 0.0001$), INSS non-stage 4 (89.0% vs. 78.4% if stage 4; $p = 0.0016$), *MYCN* amplification (85.5% vs. 77.1% if non-amplified; $p = 0.0006$), 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no LOH; $p = 0.0085$), no 11q LOH (84.8% vs. 70.9% if 11q LOH; $p = 0.0004$) and high MKI (84.5% vs. 77.5% if low-intermediate MKI; $p = 0.0098$).

We also evaluated potential predictors that occur after initial diagnosis, including early response or treatment delays/modifications. Early response was significantly associated with ≥PR at end induction (Table 1). In contrast, treatment delay or treatment modifications were not significantly associated with end-induction PR or better.

3.4. Univariate predictors of CR at end-induction or induction PD

We then assessed our secondary response end-points of CR or PD. INSS non-stage 4, *MYCN* amplification, lack of 11q LOH, high MKI and lack of MIBG avidity were the baseline variables significantly associated with higher rates of CR at end induction (Table 2). Early PD

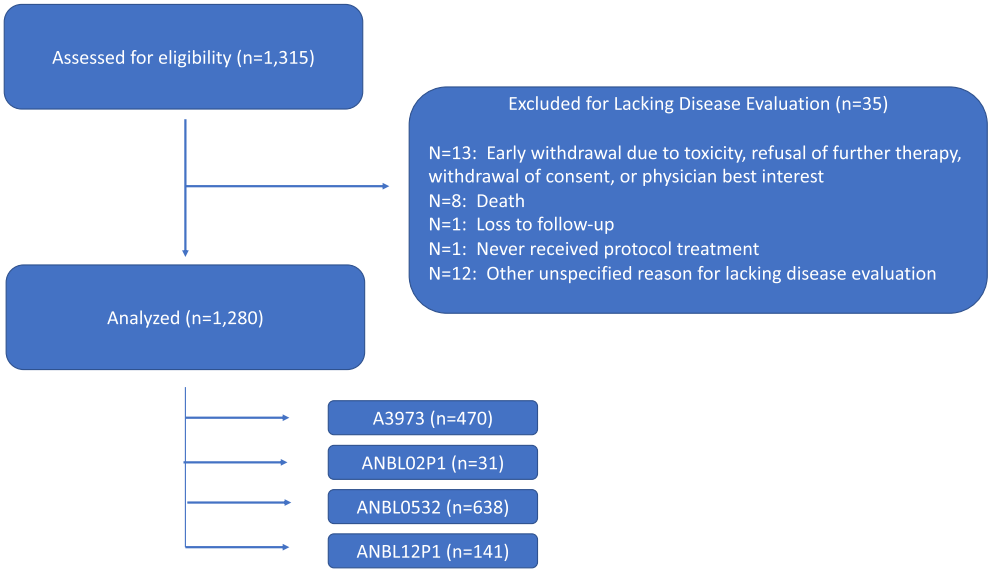

Fig. 1. CONSORT diagram of eligible and analysed subjects.

Table 1
Clinical and biological features by end-induction response (≥PR vs <PR) in patients with high-risk neuroblastoma.

Feature	All patients[b]	Partial response or better[c]	Less than partial response[c]	*p*-value[a]
	N (%)	N (%)	N (%)	
Age ≥ 18 months at diagnosis	1083 (87.20)	852 (78.67)	231 (21.33)	**0.0103**[a]
Age < 18 months at diagnosis	159 (12.80)	139 (87.42)	20 (12.58)	
Age ≥ 5 years at diagnosis	245 (19.73)	173 (70.61)	72 (29.39)	**<0.0001**[a]
Age < 5 years at diagnosis	997 (80.27)	818 (82.05)	179 (17.95)	
Male	714 (57.49)	570 (79.83)	144 (20.17)	0.9664
Female	528 (42.51)	421 (79.73)	107 (20.27)	
White race	913 (81.08)	727 (79.63)	186 (20.37)	0.5828
Non-white race	213 (18.92)	166 (77.93)	47 (22.07)	
Unknown	116	98	18	
Latino/Hispanic	131 (10.93)	101 (77.10)	30 (22.90)	0.4455
Non-Latino/Hispanic	1067 (89.07)	853 (79.94)	214 (20.06)	
Unknown	44	37	7	
INSS stage 4	1078 (86.80)	845 (78.39)	233 (21.61)	**0.0016**[a]
All other stages	164 (13.20)	146 (89.02)	18 (10.98)	
Adrenal primary	546 (46.19)	420 (76.92)	126 (23.08)	0.0281
Other primary sites	636 (53.81)	522 (82.08)	114 (17.92)	
Unknown	60	49	11	
Thoracic primary	72 (6.09)	63 (87.50)	9 (12.50)	0.0894
Other primary sites	1110 (93.91)	879 (79.19)	231 (20.81)	
Unknown	60	49	11	
Presence of bone metastasis	252 (64.45)	215 (85.32)	37 (14.68)	0.1650
Absence of bone metastasis	139 (35.55)	111 (79.86)	28 (20.14)	
Unknown	851	665	186	
Presence of bone marrow metastasis	296 (75.70)	245 (82.77)	51 (17.23)	0.5701
Absence of bone marrow metastasis	95 (24.30)	81 (85.26)	14 (14.74)	
Unknown	851	665	186	
MYCN amplified	469 (43.55)	401 (85.50)	68 (14.50)	**0.0006**[a]
MYCN non-amplified	608 (56.45)	469 (77.14)	139 (22.86)	
Unknown	165	121	44	
ALK aberrant	96 (38.71)	79 (82.29)	17 (17.71)	0.7965
ALK wild type	152 (61.29)	127 (83.55)	25 (16.45)	
Unknown	994	785	209	
Diploid	532 (53.31)	420 (78.95)	112 (21.05)	0.1976
Hyperdiploid	466 (46.69)	383 (82.19)	83 (17.81)	
Unknown	244	188	56	
LOH at 1p	215 (45.07)	184 (85.58)	31 (14.42)	**0.0085**[a]
No 1p LOH	262 (54.93)	199 (75.95)	63 (24.05)	
Unknown	765	608	157	
LOH at 11q	151 (32.40)	107 (70.86)	44 (29.14)	**0.0004**[a]
No 11q LOH	315 (67.60)	267 (84.76)	48 (15.24)	
Unknown	776	617	159	
Presence of LOH at 1p and/or 11q	324 (68.79)	261 (80.56)	63 (19.44)	0.8077
No LOH at 1p or 11q	147 (31.21)	117 (79.59)	30 (20.41)	
Unknown	771	613	158	
Unfavourable histology	1007 (96.00)	799 (79.34)	208 (20.66)	0.8007
Favourable histology	42 (4.00)	34 (80.95)	8 (19.05)	
Unknown	193	158	35	
High MKI	373 (42.00)	315 (84.45)	58 (15.55)	**0.0098**[a]
Low/intermediate MKI	515 (58.00)	399 (77.48)	116 (22.52)	
Unknown	354	277	77	
Undifferentiated/poorly differentiated	970 (95.94)	769 (79.28)	201 (20.72)	0.5713
Differentiating	41 (4.06)	34 (82.93)	7 (17.07)	
Unknown	231	188	43	
Chemotherapy modification	56 (11.74)	50 (89.29)	6 (10.71)	0.1206
No chemotherapy modification	421 (88.26)	340 (80.76)	81 (19.24)	
Unknown	765	601	164	

Table 1 (*continued*)

Feature	All patients[b]	Partial response or better[c]	Less than partial response[c]	*p*-value[a]
	N (%)	N (%)	N (%)	
MIBG avid	433 (90.97)	353 (81.52)	80 (18.48)	0.0580
MIBG non-avid	43 (9.03)	40 (93.02)	3 (6.98)	
Unknown	766	598	168	
Induction delay	162 (13.26)	140 (86.42)	22 (13.58)	0.0632
No induction delay	1060 (86.74)	851 (80.28)	209 (19.72)	
Unknown	20	–	20	
PD during early induction evaluation	41 (4.28)	7 (17.07)	34 (82.93)	**< 0.0001**[a]
No PD during early induction evaluation	917 (95.72)	743 (81.03)	174 (18.97)	
Unknown	284	241	43	
PR or better during early induction evaluation	498 (51.98)	453 (90.96)	45 (9.04)	**< 0.0001**[a]
< PR during early induction evaluation	460 (48.02)	297 (64.57)	163 (35.43)	
Unknown	284	241	43	

PR, partial response; PD, progressive disease; MKI, mitosis-karyorrhexis index; LOH, INSS, International Neuroblastoma Staging System.

[a] Statistically significant *p*-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

[b] Percentages in this column sum to 100%, with patients with unknown values listed but not included in the reported percentages.

[c] Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

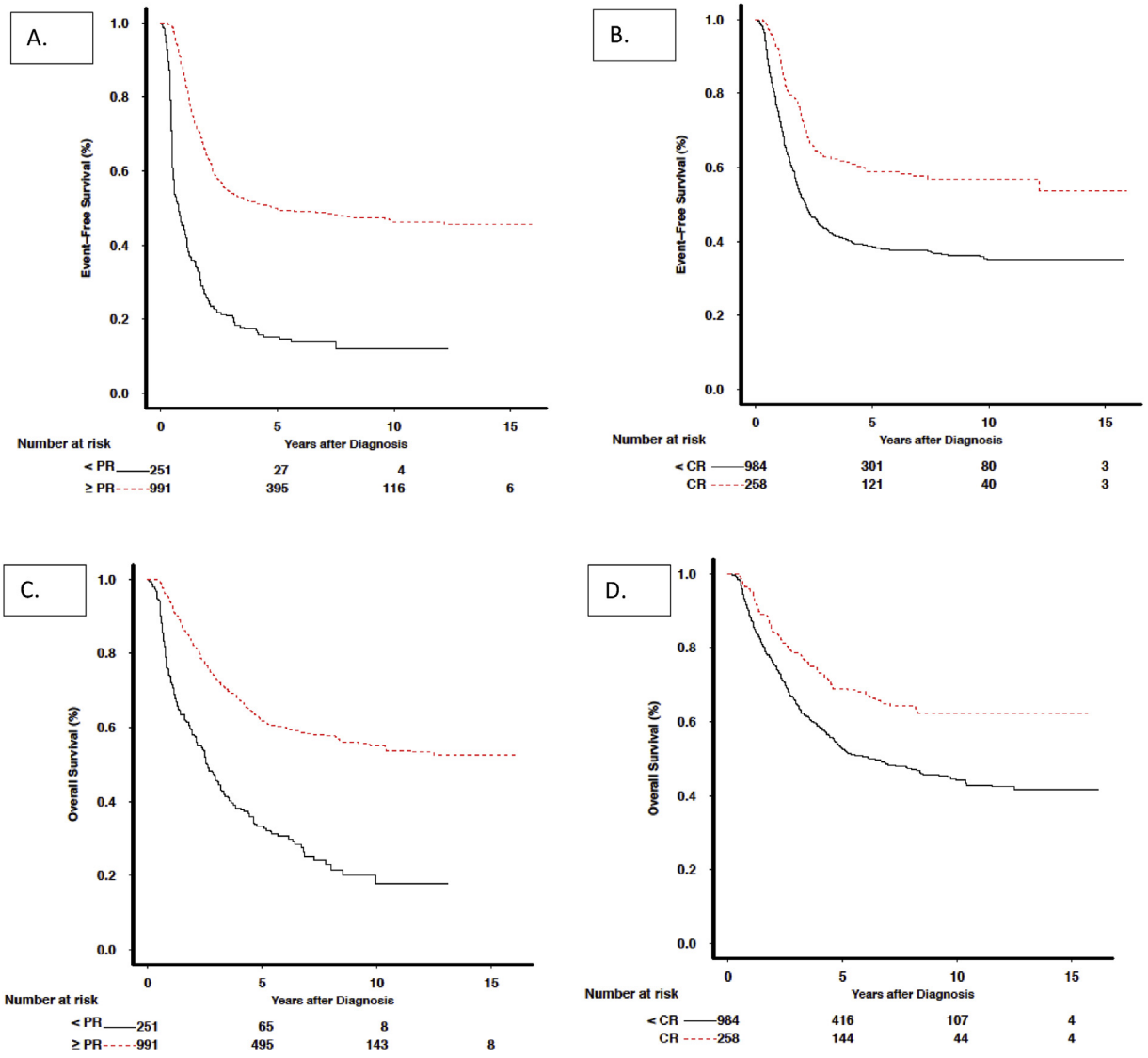

Fig. 2. **A** Event-free survival according to end-induction partial response (PR) or better vs. less than PR. **B.** Event-free survival according to end-induction complete response (CR) vs. less than CR. **C.** Overall survival according to end-induction PR or better vs. less than PR. **D.** Overall survival according to end-induction CR vs. less than CR. Log-rank test $p < 0.0001$ for all panels.

Table 2
Clinical and biological features by end-induction response (CR vs < CR) in patients with high-risk neuroblastoma.

Feature	Complete response[b]	Less than complete response[b]	*p*-value[a]
	N (%)	N (%)	
Age ≥ 18 months at diagnosis	223 (20.59)	860 (79.41)	0.6799
Age < 18 months at diagnosis	35 (22.01)	124 (77.99)	
Age ≥ 5 years at diagnosis	42 (17.14)	203 (82.86)	0.1180
Age < 5 years at diagnosis	216 (21.66)	781 (78.34)	
Male	139 (19.47)	575 (80.53)	0.1873
Female	119 (22.54)	409 (77.46)	
White race	195 (21.36)	718 (78.64)	0.2538
Non-white race	38 (17.84)	175 (82.16)	
Unknown	25	91	
Latino/Hispanic	25 (19.08)	106 (80.92)	0.5778
Non-Latino/Hispanic	226 (21.18)	841 (78.82)	
Unknown	7	37	
INSS stage 4	192 (17.81)	886 (82.19)	**< 0.0001**[a]
All other stages	66 (40.24)	98 (59.76)	
Adrenal primary	124 (22.71)	422 (77.29)	0.1363
Other primary sites	122 (19.18)	514 (80.82)	
Unknown	12	48	
Thoracic primary	11 (15.28)	61 (84.72)	0.2326
Other primary sites	235 (21.17)	875 (78.83)	
Unknown	12	48	
Presence of bone metastasis	47 (18.65)	205 (81.35)	0.0663
Absence of bone metastasis	37 (26.62)	102 (73.38)	
Unknown	174	677	
Presence of bone marrow metastasis	66 (22.30)	230 (77.70)	0.4891
Absence of bone marrow metastasis	18 (18.95)	77 (81.05)	
Unknown	174	677	
MYCN amplified	127 (27.08)	342 (72.92)	**< 0.0001**[a]
MYCN non-amplified	98 (16.12)	510 (83.88)	
Unknown	33	132	
ALK aberrant	25 (26.04)	71 (73.96)	0.6991
ALK wild type	43 (28.29)	109 (71.71)	
Unknown	190	804	
Diploid	110 (20.68)	422 (79.32)	0.8259
Hyperdiploid	99 (21.24)	367 (78.76)	
Unknown	49	195	
LOH at 1p	54 (25.12)	161 (74.88)	0.0436
No 1p LOH	46 (17.56)	216 (82.44)	
Unknown	158	607	
LOH at 11q	21 (13.91)	130 (86.09)	**0.0196**[a]
No 11q LOH	73 (23.17)	242 (76.83)	
Unknown	164	612	
Presence of LOH at 1p and/or 11q	70 (21.60)	254 (78.40)	0.3281
No LOH at 1p or 11q	26 (17.69)	121 (82.31)	
Unknown	162	609	
Unfavourable histology	220 (21.85)	787 (78.15)	0.1240
Favourable histology	5 (11.90)	37 (88.10)	
Unknown	33	160	
High MKI	98 (26.27)	275 (73.73)	**0.0066**[a]
Low/intermediate MKI	96 (18.64)	419 (81.36)	
Unknown	64	290	
Undifferentiated/poorly differentiated	208 (21.44)	762 (78.56)	0.5030
Differentiating	7 (17.07)	34 (82.93)	
Unknown	43	188	
MIBG avid	95 (21.94)	338 (78.06)	**< 0.0001**[a]
MIBG non-avid	22 (51.16)	21 (48.84)	
Unknown	141	625	

Table 2 (*continued*)

Feature	Complete response[b]	Less than complete response[b]	*p*-value[a]
	N (%)	N (%)	
Chemotherapy modification	18 (32.14)	38 (67.86)	0.1035
No chemotherapy Modification	94 (22.33)	327 (77.67)	
Unknown	146	619	
Induction delay	29 (17.90)	133 (82.10)	0.2822
No induction delay	229 (21.60)	831 (78.40)	
Unknown	–	20	
PD during early induction evaluation	–	41 (100.00)	**0.0011**[a]
No PD during early induction evaluation	190 (20.72)	727 (79.28)	
Unknown	68	216	
PR or better during early induction evaluation	146 (29.32)	352 (70.68)	**< 0.0001**[a]
< PR during early induction evaluation	44 (9.57)	416 (90.43)	
Unknown	68	216	

PR, partial response; PD, progressive disease; MKI, mitosis-karyorrhexis index; LOH, loss of heterozygosity; INSS, International Neuroblastoma Staging System.

[a] Statistically significant *p*-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

[b] Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Table 3
Clinical and biological features according to documented progressive disease during induction therapy in patients with high-risk neuroblastoma.

Feature	Progressive disease[c]	No disease progression[c]	*p*-value[a]
	N (%)	N (%)	
Age ≥ 18 months at diagnosis	99 (9.14)	984 (90.86)	0.8905
Age < 18 months at diagnosis	14 (8.81)	145 (91.19)	
Age ≥ 5 years at diagnosis	20 (8.16)	225 (91.84)	0.5701
Age < 5 years at diagnosis	93 (9.33)	904 (90.67)	
Male	60 (8.40)	654 (91.60)	0.3221
Female	53 (10.04)	475 (89.96)	
White race	83 (9.09)	830 (90.91)	0.5759
Non-white race	22 (10.33)	191 (89.67)	
Unknown	8	108	
Latino/Hispanic	13 (9.92)	118 (90.08)	0.6460
Non-Latino/Hispanic	93 (8.72)	974 (91.28)	
Unknown	7	37	
INSS stage 4	100 (9.28)	978 (90.72)	0.5755
All other stages	13 (7.93)	151 (92.07)	
Adrenal primary	57 (10.44)	489 (89.56)	0.1800
Other primary sites	52 (8.18)	584 (91.82)	
Unknown	4	56	
Thoracic primary	4 (5.56)	68 (94.44)	0.2672
Other primary sites	105 (9.46)	1005 (90.54)	
Unknown	4	56	
Presence of bone metastasis	21 (8.33)	231 (91.67)	0.3042
Absence of bone metastasis	16 (11.51)	123 (88.49)	
Unknown	76	775	
Presence of bone marrow metastasis	27 (9.12)	269 (90.88)	0.6840
Absence of bone marrow metastasis	10 (10.53)	85 (89.47)	
Unknown	76	775	
MYCN amplified	47 (10.02)	422 (89.98)	0.2224
MYCN non-amplified	48 (7.89)	560 (92.11)	
Unknown	18	147	
ALK aberrant	10 (10.42)	86 (89.58)	0.1276
ALK wild type	8 (5.26)	144 (94.74)	
Unknown	95	899	

(*continued on next page*)

Table 3 (*continued*)

Feature	Progressive disease[c]	No disease progression[c]	*p*-value[a]
	N (%)	N (%)	
Diploid	53 (9.96)	479 (90.04)	0.2658
Hyperdiploid	37 (7.94)	429 (92.06)	
Unknown	23	221	
LOH at 1p	14 (6.51)	201 (93.49)	0.9919
No 1p LOH	17 (6.49)	245 (93.51)	
Unknown	82	683	
LOH at 11q	15 (9.93)	136 (90.07)	**0.0491**[a]
No 11q LOH	16 (5.08)	299 (94.92)	
Unknown	82	694	
Presence of LOH at 1p and/or 11q	23 (7.10)	301 (92.90)	0.5017
No LOH at 1p or 11q	8 (5.44)	139 (94.56)	
Unknown	82	689	
Unfavourable histology	98 (9.73)	909 (90.27)	**0.7905**[b]
Favourable histology	3 (7.14)	39 (92.86)	
Unknown	12	181	
High MKI	37 (9.92)	336 (90.08)	0.3621
Low/intermediate MKI	42 (8.16)	473 (91.84)	
Unknown	34	320	
Undifferentiated/poorly differentiated	89 (9.18)	881 (90.82)	**0.7851**[b]
Differentiating	4 (9.76)	37 (90.24)	
Unknown	20	211	
MIBG avid	34 (7.85)	399 (92.15)	**0.3510**[b]
MIBG non-avid	1 (2.33)	42 (97.67)	
Unknown	78	688	
Chemotherapy modification	5 (8.93)	51 (91.07)	0.7639
No chemotherapy modification	43 (10.21)	378 (89.79)	
Unknown	65	700	
Induction delay	10 (6.17)	152 (93.83)	0.4587
No induction delay	83 (7.83)	977 (92.17)	
Unknown	20	–	
PD during early induction evaluation	27 (65.85)	14 (34.15)	**< 0.0001**[b,a]
No PD during early induction evaluation	59 (6.43)	858 (93.57)	
Unknown	27	257	
PR or better during early induction evaluation	22 (4.42)	476 (95.58)	**< 0.0001**[a]
< PR during early induction evaluation	64 (13.91)	396 (86.09)	
Unknown	27	257	

PR, partial response; PD, progressive disease; MKI, mitosis-karyorrhexis index; LOH, loss of heterozygosity; INSS, International Neuroblastoma Staging System.

[a] Statistically significant *p*-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

[b] Fisher's exact test was used in place of the chi-square test as expected counts were <5.

[c] Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

and early PR were associated with lower and higher rates of subsequent CR, respectively.

End-induction PD was reported in 113 of 1242 (9.1%) patients. 11q LOH was the sole baseline variable associated with PD at end induction (Table 3). Among response-based variables, early PD and early PR were significantly associated with higher and lower rates of end-induction PD, respectively. OS of patients who experienced PD was poor. The 3-year OS estimates were 31.2 ± 4.3% (early or end-induction PD) versus 71.4 ± 1.4% (no PD; log-rank test *p*-value< 0.0001; Fig. 3).

3.5. Factors associated with early responses to induction chemotherapy

We also assessed early PR and early PD as secondary outcomes of interest. Early PR was seen in 520 of 996 (52.2%) and early PD was seen in 41 of 996 (4.1%) patients. Patients with early PD were allowed to stay on protocol therapy at the discretion of their treating physician. Younger age at diagnosis (using either the 18-month or 5-year cut-offs), INSS non-stage 4, *MYCN* amplification, 1p LOH, lack of 11q LOH and higher MKI were significantly associated with higher rates of

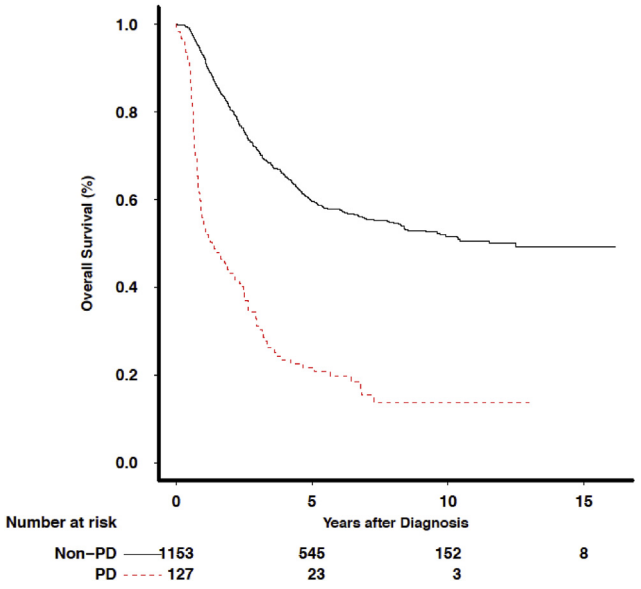

Fig. 3. Overall survival according to PD (both early and end-induction PD) vs no PD during induction. Log-rank test $p < 0.0001$. PD, progressive disease.

early PR (Table 4). There were no variables significantly associated with early PD (Table 4).

3.6. Multivariable analyses

Multivariable logistic regression models were constructed to identify variables associated with end-induction PR and CR, starting from the variables that were statistically significant in the univariate analyses (Table 5).

Only lack of 11q LOH remained significantly associated with end-induction PR [OR = 1.962; 95% confidence interval (CI): 1.104, 3.487] compared to reference group with 11q LOH ($p = 0.0216$). A separate model excluding 1p and 11q (due to missing data in >50% of the overall cohort and 100% of patients enrolled on ANBL02P1) and retaining age, stage, *MYCN* status and MKI showed that non-stage 4 disease was the sole significant predictor of higher likelihood of end-induction PR (OR = 2.520; 95% CI: 1.380, 4.602) compared to the reference group with stage 4 disease ($p = 0.0026$).

Table 4
Clinical and biological features by early response assessment performed mid-induction therapy in patients with high-risk neuroblastoma.

Feature	Early PD[c]	No early PD[c]	*p*-value[a]	Early PR or better[d]	< PR at early time point[d]	*p*-value[a]
	N (%)	N (%)		N (%)	N (%)	
Age ≥ 18 months at diagnosis	35 (4.02)	835 (95.98)	0.6964	437 (50.23)	433 (49.77)	**0.0010**[a]
Age < 18 months at diagnosis	6 (4.76)	120 (95.24)		83 (65.87)	43 (34.13)	
Age ≥ 5 years at diagnosis	10 (4.83)	197 (95.17)	0.5610	79 (38.16)	128 (61.84)	**< 0.0001**[a]
Age < 5 years at diagnosis	31 (3.93)	758 (96.07)		441 (55.89)	348 (44.11)	
Male	26 (4.56)	544 (95.44)	0.4136	302 (52.98)	268 (47.02)	0.5718
Female	15 (3.52)	411 (96.48)		218 (51.17)	208 (48.83)	
White race	31 (4.17)	712 (95.83)	0.7216	384 (51.68)	359 (48.32)	0.5605
Non-white race	6 (3.57)	162 (96.43)		91 (54.17)	77 (45.83)	
Unknown	4	81		45	40	
Latino/Hispanic	4 (3.85)	100 (96.15)	1.0000[b]	57 (54.81)	47 (45.19)	0.6027
Non-Latino/Hispanic	36 (4.22)	818 (95.78)		445 (52.11)	409 (47.89)	
Unknown	1	37		18	20	
INSS stage 4	36 (4.17)	827 (95.83)	0.8238	429 (49.71)	434 (50.29)	**< 0.0001**[a]
All other stages	5 (3.76)	128 (96.24)		91 (68.42)	42 (31.58)	
Adrenal primary	21 (4.90)	408 (95.10)	0.3565	220 (51.28)	209 (48.72)	0.6611
Other primary sites	19 (3.68)	497 (96.32)		272 (52.71)	244 (47.29)	
Unknown	1	50		28	23	
Thoracic primary	2 (3.45)	56 (96.55)	1.0000[b]	27 (46.55)	31 (53.45)	0.3858
Other primary sites	38 (4.28)	849 (95.72)		465 (52.42)	422 (47.58)	
Unknown	1	50		28	23	
Presence of bone metastasis	2 (1.18)	167 (98.82)	0.1009[b]	88 (52.07)	81 (47.93)	0.4448
Absence of bone metastasis	5 (5.38)	88 (94.62)		53 (56.99)	40 (43.01)	
Unknown	34	700		379	355	
Presence of bone marrow metastasis	4 (2.04)	192 (97.96)	0.3731[b]	107 (54.59)	89 (45.41)	0.6645
Absence of bone marrow metastasis	3 (4.55)	63 (95.45)		34 (51.52)	32 (48.48)	
Unknown	34	700		379	355	
MYCN amplified	18 (4.85)	353 (95.15)	0.4812	257 (69.27)	114 (30.73)	**< 0.0001**[a]
MYCN non-amplified	19 (3.87)	472 (96.13)		203 (41.34)	288 (58.66)	
Unknown	4	130		60	74	

(*continued on next page*)

Table 4 (*continued*)

Feature	Early PD[c]	No early PD[c]	*p*-value[a]	Early PR or better[d]	< PR at early time point[d]	*p*-value[a]
	N (%)	N (%)		N (%)	N (%)	
ALK aberrant	2 (2.90)	67 (97.10)	0.6282[b]	50 (72.46)	19 (27.54)	0.2407
ALK wild type	2 (1.71)	115 (98.29)		75 (64.10)	42 (35.90)	
Unknown	37	773		395	415	
Diploid	13 (3.22)	391 (96.78)	0.2159	217 (53.71)	187 (46.29)	0.7849
Hyperdiploid	19 (4.96)	364 (95.04)		202 (52.74)	181 (47.26)	
Unknown	9	200		101	108	
LOH at 1p	7 (3.83)	176 (96.17)	0.9135	123 (67.21)	60 (32.79)	**< 0.0001**[a]
No 1p LOH	8 (3.62)	213 (96.38)		102 (46.15)	119 (53.85)	
Unknown	26	566		295	297	
LOH at 11q	6 (4.84)	118 (95.16)	0.3852[b]	54 (43.55)	70 (56.45)	**0.0012**[a]
No 11q LOH	8 (2.97)	261 (97.03)		164 (60.97)	105 (39.03)	
Unknown	27	576		302	201	
Presence of LOH at 1p and/or 11q	10 (3.65)	264 (96.35)	1.0000[b]	161 (58.76)	113 (41.24)	0.0378
No LOH at 1p or 11q	5 (4.03)	119 (95.97)		59 (47.58)	65 (52.42)	
Unknown	26	572		300	298	
Unfavourable histology	35 (4.35)	769 (95.65)	0.3981[b]	427 (53.11)	377 (46.89)	0.4885
Favourable histology	–	38 (100.00)		18 (47.37)	20 (52.63)	
Unknown	6	148		75	79	
High MKI	12 (3.93)	293 (96.07)	0.8248	200 (65.57)	105 (34.43)	**< 0.0001**[a]
Low/intermediate MKI	18 (4.27)	404 (95.73)		193 (45.73)	229 (54.27)	
Unknown	11	258		127	142	
Undifferentiated/poorly differentiated	33 (4.13)	766 (95.87)	0.2718[b]	426 (53.32)	373 (46.68)	0.0533
Differentiating	2 (8.33)	22 (91.67)		8 (33.33)	16 (66.67)	
Unknown	6	167		86	87	
MIBG avid	7 (2.27)	301 (97.73)	1.0000[b]	187 (60.71)	121 (39.29)	0.1225
MIBG non-avid	–	22 (100.00)		17 (77.27)	5 (22.73)	
Unknown	34	632		316	350	
Chemotherapy modification	–	14 (100)	1.0000[b]	11 (78.57)	3 (21.43)	0.0623
No chemotherapy modification	9 (2.88)	303 (97.12)		166 (53.21)	146 (46.79)	
Unknown	32	638		343	327	
Induction delay	3 (3.09)	94 (96.91)	0.5093[b]	55 (56.70)	42 (43.30)	0.4728
No induction delay	18 (2.06)	854 (97.94)		461 (52.87)	411 (47.13)	
Unknown	20	7		4	23	

PR, partial response; PD, progressive disease; MKI, mitosis-karyorrhexis index; LOH, loss of heterozygosity; INSS, International Neuroblastoma Staging System.

[a] Statistically significant *p*-values have been highlighted, after adjustment for multiple comparisons using a family-wise error rate of 0.05.

[b] Fisher's exact test was used in place of the chi-square test as expected counts were <5.

[c] Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

[d] Percentages in each row of these two columns sum to 100% across these two columns, with patients with unknown values listed but not included in the reported percentages.

Using CR at end induction as the outcome of interest, we constructed three separate models (Table 5). The first model used all significant univariate predictors of CR. Only 99 patients had data available for all these variables, and no variables were significant on multivariate testing. Acknowledging the impact of missing data on this analysis, we then constructed a model excluding MIBG avidity. The resulting model included 408 patients and showed that non-stage 4 disease and *MYCN* amplification were associated with significantly higher likelihood of end-induction CR. We repeated the analysis excluding 11q status and obtained similar results.

4. Discussion

In this comprehensive assessment of response to induction therapy for patients with high-risk neuroblastoma treated between 2001 and 2015, we confirmed that end-induction responses of PR or better or CR are associated with superior EFS and OS. We observed that clinical and biological factors present at the time of diagnosis of high-risk neuroblastoma are associated with differential responses to induction therapy. Features generally viewed as more favourable (younger age and lower stage) and others generally viewed as unfavourable (*MYCN* amplification, 1p LOH and high MKI)

Table 5
Multivariable logistic regression models of end-induction response in high-risk neuroblastoma.

Predictors of partial response or better				
Feature	With 1p and 11q (n = 407)		Without 1p and 11q (n = 855)	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (<5 years vs. ≥5 years[a])	1.611 (0.876, 2.963)	0.1252	1.458 (0.951, 2.235)	0.0838
INSS stage (non-stage 4 vs. stage 4[a])	1.378 (0.615, 3.087)	0.4365	2.520 (1.380, 4.602)	**0.0026**
MYCN status (non-amplified vs. amplified[a])	1.061 (0.496, 2.269)	0.8795	0.716 (0.471, 1.087)	0.1170
1p LOH (No LOH vs. 1p LOH[a])	0.772 (0.419, 1.425)	0.4085	–	–
11q LOH (No LOH vs. 11q LOH[a])	1.962 (1.104, 3.487)	**0.0216**	–	–
MKI (low/intermediate vs. high[a])	0.784 (0.417, 1.474)	0.4492	0.846 (0.555, 1.287)	0.4343

Predictors of complete response						
Feature	With MIBG (n = 99)		Without MIBG (n = 408)		Without MIBG and 11q (n = 855)	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
INSS stage (non-stage 4 vs. stage 4[a])	1.607 (0.420, 6.155)	0.4887	2.015 (1.080, 3.760)	**0.0276**	2.916 (1.965, 4.327)	**<0.0001**
MYCN status (non-amplified vs. amplified[a])	0.373 (0.111, 1.252)	0.1105	0.318 (0.165, 0.612)	**0.0006**	0.491 (0.491, 0.333)	**0.0003**
11q LOH (No LOH vs. 11q LOH[a])	2.197 (0.594, 8.128)	0.2383	1.128 (0.587, 2.167)	0.7188	–	–
MKI (low/intermediate vs. high[a])	1.262 (0.409, 3.893)	0.6859	1.393 (0.772, 2.512)	0.2708	0.958 (0.651, 1.409)	0.8258
MIBG avidity (non-avid vs. avid[a])	3.405 (0.837, 13.859)	0.0871	–	–	–	–

MKI, mitosis-karyorrhexis index; LOH, loss of heterozygosity; INSS, International Neuroblastoma Staging System; CI, confidence interval.
[a] Indicates the reference level for each variable.

were associated with more favourable induction response. Interestingly, 11q LOH was shown to be a significant predictor of PD, and lack of 11q LOH was associated with both higher rates of end-induction CR and of end-induction PR or better, the latter even after controlling for other factors. We also noted that end-induction response was associated with response assessments performed earlier in the course of induction. Another key finding was that treatment delays or modifications were not associated with a lower rate of induction response. We hypothesised that treatment delays would lead to inferior end-induction responses, and our definition sought to capture patients with fairly extreme delays in protocol directed therapy. The fact that this degree of delay did not affect outcome supports current practice, in the context of intensive multimodal therapy, that allows patients to fully recover between treatment cycles, before surgery and before proceeding to post-induction therapies. Whether there is an association between treatment delays/dose modifications and long-term outcomes is outside the scope of the current analysis focused on induction response.

Status at 11q appeared to be an important determinant of response to induction therapy. 11q LOH has been previously identified as an adverse prognostic feature in patients with neuroblastoma and is often found in *MYCN*-non-amplified high-risk neuroblastoma [22]. 11q LOH is commonly found with other segmental chromosomal aberrations such as 1p deletion and 17q gain, and tumours with segmental chromosomal aberrations are much more frequently seen in patients with high-risk neuroblastoma, as opposed to numerical chromosomal aberrations, which are more frequently seen in patients with non-high-risk neuroblastoma [23]. The role of 11q loss in mediating adverse outcomes in neuroblastoma is largely unknown, although our results suggest that 11q loss may be a marker of general chemoresistance. Proposed mechanisms of the impact of 11q loss on outcomes include loss of tumour suppressor genes (such as *CADM1*, *ATM* or *H2AFX*) or microRNAs (such as miR4301, miR125b-1, let-7a or miR100) versus the deletion of multiple genes and creation of a tumourigenic haploinsufficient state [24].

Both INSS non-stage 4 (INSS stage 1–3 and 4S) disease and *MYCN* amplification were independently associated with CR at end induction. Patients with non-stage 4 disease were twice as likely to have a CR when compared with patients with metastatic disease (INSS stage 4). Clinical stage has been previously shown to independently associate with outcome. In a prospective analysis of the INSS, the 4-year OS for patients >12 months with stage 1, 2A, 2B and 3 disease was 100% compared with 48.5% in patients with stage 4 disease ($p < 0.0001$) [25]. Similarly, amplification of the *MYCN* oncogene is a well-documented adverse prognostic feature that correlates with high-risk disease and is present in approximately 20% of neuroblastoma tumours [26–28]. The finding of higher response rates in patients with *MYCN*-amplified tumours is noteworthy as we show that not all unfavourable prognostic factors are associated with unfavourable response to induction chemotherapy. *MYCN*-amplified tumours often exhibit a greater degree of tumour necrosis in response to chemotherapy than *MYCN*-non-amplified tumours [29]. The higher proliferative rate associated with *MYCN* amplification may result in greater chemosensitivity, a hypothesis supported by higher response rates in patients with tumours with a high MKI.

Our analysis has certain strengths and weaknesses worthy of further note. We leveraged a large data set with robust centralised assessment of baseline *MYCN* status and tumour histologic features. In addition, measurement of response using the 1993 version of the INRC was used across all 4 studies included in this analysis. We evaluated several domains of induction response and used a strategy to control for multiple testing. However, given the size of the analytical cohort, central review of response was not possible. This weakness is noteworthy given that the included patients were diagnosed over a >10-year period of time when imaging approaches evolved. For example, MIBG imaging has become routine and is now almost exclusively performed with ^{123}I-MIBG as the preferred imaging agent compared with prior usage of ^{131}I-MIBG or technetium-99 bone scan. Similarly, fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is now more widely used for patients with MIBG non-avid tumours. It is possible that lack of FDG-PET imaging to fully evaluate these patients in earlier studies may have yielded the finding that patients with MIBG non-avid disease had differing CR rates. We also note that the induction regimens used in each of the four trials were not uniform, although all were intensive multiagent regimens. Data were missing in >50% of patients for several variables, including 11q status, for which data were missing disproportionately in patients enrolled on earlier trials in our analysis. We attempted to mitigate this limitation by constructing multivariable models with and without these variables, but a potential bias may remain. Finally, we acknowledge that our definition of treatment delay was an arbitrary (though *a priori*) definition and that other cut points to define delay could be considered.

5. Conclusions

The clinical and biological factors included in this analysis of induction response are the factors historically considered, and supported by statistical evidence, for assigning a risk group classifier and subsequent treatment. However, within the high-risk group, largely defined as patients with *MYCN* amplification or children older than 18 months with metastatic disease, reliable predictors of overall response to high-risk therapy and/or outcome are lacking. Efforts have been made to identify a so-called 'ultra-high-risk' group of patients with a low predicted OS with standard high-risk therapies who may benefit from augmentation of traditional high-risk therapies to include targeted or alternative interventions. Our analysis demonstrates that patients who develop progressive disease during induction therapy are at high risk of subsequent death and should be prioritised for novel salvage approaches. In previous studies, the response to induction therapy appears to be a sensitive predictor of subsequent risk of relapse in patients with high-risk neuroblastoma [8–10]. Our investigation represents the largest cohort of patients with high-risk neuroblastoma analysed for predictive biomarkers of induction response. Identification of reliable predictors of response to high-risk therapies has the potential to further refine our risk classifiers and potentially spare some patients from the significant late effects of traditional high-risk therapies [30].

Conflict of interest statement

The authors have no conflicts of interest to report.

Disclaimers

None.

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Appendix A. Supplementary data

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