The evaluation of induction chemotherapy regimens for high-risk neuroblastoma in South African children

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Abstract

Achieving remission after induction therapy in high-risk neuroblastoma (HR-NB) is of significant prognostic importance. This study investigated remission after induction-chemotherapy using three standard neuroblastoma protocols in the South African (SA) setting. Retrospective data of 261 patients with HR-NB diagnosed between January 2000 and December 2016, who completed induction chemotherapy with standard treatment protocols were evaluated. The treatment protocols were either OPEC/OJEC or the St Jude NB84 protocol (NB84) or rapid COJEC (rCOJEC). The postinduction metastatic complete remission (mCR) rate, 2-year overall survival (OS) and 2-year event free survival (EFS) were determined as comparative denominators. The majority (48.3%; $n = 126$) received OPEC/OJEC, while 70 patients received (26.8%) rCOJEC and 65 (24.9%) NB84. Treatment with NB84 had the best mCR rate (36.9%), followed by OPEC/OJEC (32.5%) and rCOJEC (21.4%). The 2-year OS of treatment with NB84 was 41% compared to OPEC/OJEC (35%) and rCOJEC (24%) ($p = 0.010$). The 2-year EFS of treatment with NB84 was 37% compared to OPEC/OJEC (35%) and rCOJEC (18%) ($p = 0.008$). OPEC/OJEC had the least treatment-related deaths (1.6%) compared to rCOJEC (7.1%) and NB84 (7.5%) ($p = 0.037$). On multivariate analysis LDH ($p = 0.023$), ferritin ($p = 0.002$) and INSS stage ($p = 0.006$) were identified as significant prognostic factors for OS. The induction chemotherapy was not significant for OS ($p = 0.18$), but significant for EFS ($p = 0.08$) Treatment with NB84 achieved better mCR, OS and EFS, while OPEC/OJEC had the least treatment-related deaths. In resource-constrained settings, OPEC/OJEC is advised as induction chemotherapy in HR-NB due to less toxicity as reflected in less treatment-related deaths.

Keywords: High risk, induction chemotherapy, neuroblastoma, South Africa

Introduction

Achieving metastatic remission after induction chemotherapy in high-risk (HR) neuroblastoma (NB) is of prognostic significance, even though the treatment is of high intensity with potentially severe toxicity.[1,2] NB induction chemotherapy is characterized by the delivery of increasingly intensive multimodal therapies. European approaches under the EU-20592 or CCLGNB-1990-11 protocols have studied decreasing time by reducing administration of OPEC/OJEC from 28-day cycles to 21-day cycles.[3] Rapid COJEC (rCOJEC) chemotherapy is highly intensive therapy, administered every 10 days regardless of toxicity.[3] Although this ensures that a patient reaches the consolidation treatment phase sooner, there is a greater likelihood of chemotherapy-induced toxicity.[4]

South African doxorubicin-containing protocols approaches are based on North American protocols such as the Memorial Sloan Kettering Hospital N6 protocol,[5] and the St Jude NB84 protocol.[5] In the N6 protocol, seven cycles have resulted in either complete remission (CR) or very good partial response (VGPR) in 87% of patients. In the N7 and N8 protocols, a reduction from seven to five cycles of chemotherapy have resulted in outcomes of 79% CR or VGPR and less toxicity in 87 patients.[5]

When comparing the European induction protocols OPEC/OJEC and rCOJEC, a Cochrane review has concluded there is no clear difference regarding the efficacy obtaining a complete response, treatment-related mortality, overall survival and event-free survival.[4] It was concluded that prospective trials are needed as there is low level of evidence and due to the changes in risk classifications during the trial periods.[4] The review relied mainly on the CCLG-ENSG-5 randomized controlled trial of 262 patients with HR-NB.[6] In this study, 132 patients were randomized to receive OPEC/OJEC and 130 patients to receive rCOJEC induction chemotherapy.[6] Pearson et al. concluded that there was an increasing difference in EFS after three years with the rCOJEC induction protocol.[6] With the same cumulative dose, rCOJEC at 10-day cycles had better 10-year EFS (27%) versus a 21-day cycle (18%) ($p = 0.085$). The hypothesis was that earlier initiation of myeloablative therapy contributed to improved outcome[6] and could benefit patients in countries with access to autologous stem cell transplant services.

Limited information is available comparing doxorubicin-containing and nondoxorubicin-containing regimens. The objective of the SIOPEN randomization of modified N5-MSKCC induction protocol with rCOJEC in the HR-NBL-1.7/SIOPEN study was to compare these regimens.[7] The study concluded that rCOJEC was less toxic and there was no difference in the postinduction remission rates, OS and EFS.[7]

In resource-limited settings, with suboptimal supportive care, high-intensity chemotherapy poses a risk of increased morbidity and mortality.[8] Challenges include

inconsistent access to blood products, limited antimicrobial agents, access to intensive care units and the high chemotherapy costs.[8] Malnutrition and advanced disease also impact on the choice of regimen as they both may independently contribute to poorer outcomes.[8] It is important to select a regimen with the highest remission rate and the most favorable toxicity profile for the local setting.[8]

The treatment of HR-NB in SA has been administered according to various protocols and institutional experience.[9] This study investigated remission after standard induction NB chemotherapy in SA POUs as the South African Children's Cancer Study Group (SACCSG) aims to create a standardized prospective treatment protocol based on evidence generated by retrospective studies regarding management of NB in SA.

Materials and methods

Patient population

South Africa is a middle-income country with marked disparities between the resources of POUs. Patients with HR-NB were identified retrospectively from 10 dedicated pediatric oncology units (POUs). The study population included new cases of HR-NB diagnosed from January 2000 to December 2016. High-risk disease was defined by the presence of metastatic disease, unfavorable histology, a raised serum LDH and ferritin, amplified MYCN and adverse genetics based on the Children's Oncology Group (COG) classification system (supporting information Appendix A) and the International Neuroblastoma Risk Group (INRG) consensus pretreatment classification scheme (supporting information Appendix B). Cases were confirmed by core biopsy, fine needle aspirate or NB-defining imaging with NB infiltration of the bone marrow and elevated urine catecholamine levels.

Method

There were 354 patients included with high risk (HR) disease, of whom 93 were excluded, either because of treatment abandonment during induction, or because they were palliated from diagnosis, or the regimen cohorts were too small to be representa-tive and/or because they were treated with a nonstandard induction regimen for HR-NB. The 261 remaining patients received either St Jude NB84 protocol, OPEC/OJEC or rCOJEC as induction regimens (flow diagram Figure 1).

Data collection and analysis

Researchers from participating centers conducted retrospective chart reviews and entered data on Excel spreadsheets after ethical approval was granted. The data were linked to a unique study number and data analysis was anonymous.

Staging was determined according to the International Neuroblastoma Staging System (INSS). Metastatic remission was defined as complete remission (mCR) according to the International Neuroblastoma Response Criteria (INRC) revised in 1993 and 2012 (supporting information Appendix C).[10,11] Death before the end of induction was defined as induction failure. Nutritional parameters were applied according to WHO definitions.[12]

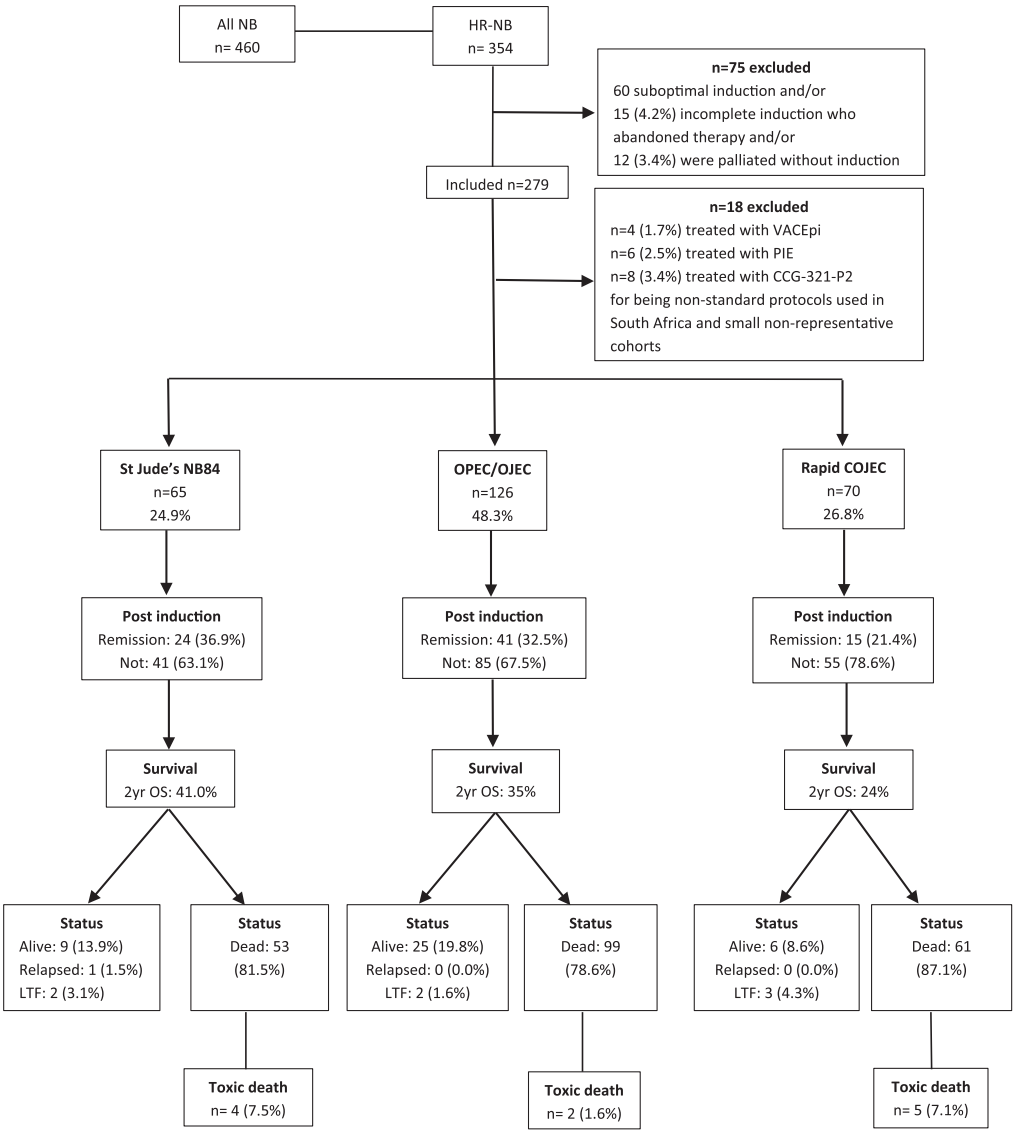

Figure 1. Flow diagram 1: Induction chemotherapy for high-risk neuroblastoma (HR-NB) in South Africa 2000–2016.

Abandonment of treatment was defined as the failure to start therapy or complete curative therapy after missing therapy for four or more consecutive weeks. Patients considered to be lost-to-follow-up were defined as those who did not return for follow-up after curative treatment for one year and who were unreachable despite efforts to contact them.

Chemotherapy regimens

Induction regimens included OPEC/OJEC (Carboplatin, Cisplatin, Etoposide, Cyclophosphamide and Vincristine),[4] the St Jude NB84 protocol (Cisplatin, Etoposide, Doxorubicin

and Cyclophosphamide)[13] and rCOJEC (Carboplatin, Cisplatin, Etoposide, Cyclophos-phamide and Vincristine).[4]

Statistical analysis

All analyses were performed in R version 3.4.4 (R foundation for Statistical Computing, Vienna, Austria).[14] Data were summarized as percentages and compared between subgroups using the chi-squared test (χ^2). EFS and OS were computed and visualized by Kaplan-Meier curves. Median EFS and OS, together with 95% confidence intervals (CI) were reported.

Differences between survival curves by chemotherapy group were assessed by log-rank test. Additionally, simple and multiple Cox regression models were built to determine the effect of various prognostic factors. A full multiple Cox regression model demonstrated the effect of chemotherapy on EFS and OS, respectively, after correction for the other prognostic factors. Similarly, simple and multiple logistic regression models were constructed to assess the effect of chemotherapy on metastatic complete remission while correcting for other factors.

Due to the retrospective methodology, numerous data on prognostic factors were not available and stated per category. Assuming data were missing at random, multiple imputation with chained equations were performed to correct for missing data. The imputation models included all variables in the analysis. Ten imputed data sets were generated and analyzed in Cox and logistic regression models as described above. Results of the imputed data analyses were pooled to obtain parameter estimates and confidence intervals.

Descriptive and simple comparisons of patients with or without complete metastatic remission were on the raw un-imputed data, while all models were based on multiple imputation, as stated in each table.

Results

Two hundred and sixty-one patients were eligible for inclusion in the analysis: 126 (48.3%) treated with OPEC/OJEC, 70 (26.8%) with rCOJEC and 65 (24.9%) were treated with the NB84 protocol. Table 1 provides the demographic data, the high-risk factors per treatment protocol and disease profile of the groups. There was a slight male predominance with a male:female ratio of 1:0.89. The majority (58.2%) of patients were in the 18–60 months category and median age was 36.1 months (interquartile range 20.2–55.7).

Outcomes

A total of 80 (30.7%) HR patients were in mCR post-induction chemotherapy. The highest mCR was obtained by treatment with NB84 (36.9%), followed by OPEC/OJEC (32.5%) and rCOJEC with 21.4% ($p = 0.12$). Treatment with NB84 had the best 2-year OS of 41% (95% CI, 30%–56%) compared to OPEC/OJEC with 35% (95% CI, 27.0%–45.0%), while OJEC/OPEC performed better than rCOJEC with 24% (95% CI, 16.0%–38.0%, $p = 0.010$) (see Figure 2). Treatment with NB84 had superior 2-year EFS

Table 1. Disease profiles per cohort.

	Total N (%)	St Jude NB84 N (%)	OPEC/OJEC N (%)	Rapid COJEC N (%)
Sex				
Male	138 (52.9%)	31/65 (47.7%)	66/126 (52.4%)	41/70 (58.6%)
Female	123 (47.1%)	34/65 (52.3%)	60/126 (47.6%)	29/70 (41.4%)
Age				
0 – 18 m	51 (19.5%)	14/65 (21.5%)	28/126 (22.2%)	9/70 (12.9%)
18.1 – 60 m	152 (58.2%)	31/65 (47.7%)	76/126 (60.3%)	45/70 (64.3%)
> 60 m	58 (22.2%)	20/65 (30.8%)	22/126 (17.5%)	16/70 (22.9%)
INSS				
Stage 4	223 (85.4%)	48/65 (73.8%)	111/126 (88.1%)	64/70 (91.4%)
Other stage	38 (14.6%)	17/65 (26.2%)	15/126 (11.9%)	6/70 (8.6%)
LDH				
< 750	87 (33.3%)	34/65 (52.3%)	33/122 (27.0%)	20/62 (32.3%)
> 750	162 (62.1%)	31/65 (47.7%)	89/122 (73.0%)	42/62 (67.7%)
Unknown	12 (4.6%)			
Ferritin				
< 120	50 (19.2%)	18/52 (34.6%)	25/88 (28.4%)	7/49 (14.3%)
> 120	139 (53.3%)	34/52 (65.4%)	63/88 (71.6%)	42/49 (85.7%)
Unknown	72 (27.6%)			
INPC				
Favorable	27 (10.3%)	1/8 (12.5%)	23/85 (27.1%)	3/38 (7.9%)
Unfavorable	104 (39.8%)	7/8 (87.5%)	62/85 (72.9%)	35/38 (92.1%)
Unknown	130 (49.8%)			
MYCN				
Nonamplified	38 (14.6%)	4/11 (36.4%)	26/81 (32.1%)	8/25 (32.0%)
Amplified/extra copies	79 (30.3%)	7/11 (63.6%)	55/81 (67.9%)	17/25 (68.0%)
Unknown	144 (55.2%)			
WFA				
> -1 SD	116 (44.4%)	20/45 (44.4%)	64/94 (68.1%)	32/55 (58.2%)
-1SD to -2 SD	41 (15.7%)	8/45 (17.8%)	19/94 (20.2%)	14/55 (25.5%)
< -2SD	37 (14.2%)	17/45 (37.8%)	11/94 (11.7%)	9/55 (16.4%)
Unknown	67 (25.7%)			
HFA				
> -1 SD	97 (37.2%)	16/45 (35.6%)	59/93 (63.4%)	22/52 (42.3%)
-1SD to -2 SD	30 (11.5%)	6/45 (13.3%)	14/93 (15.1%)	10/52 (19.2%)
< -2SD	63 (24.1%)	23/45 (51.1%)	20/93 (21.5%)	20/52 (38.5%)
Unknown	71 (27.0%)			

LDH – lactate dehydrogenase; INPC – International neuroblastoma pathology classification; INSS – International neuroblastoma staging system; WFA – weight for age (z-score); HFA – height for age (z-score); SD – standard deviations.

of 37% (95% CI, 26%–52%) compared to OPEC/OJEC with 35% (27–45%) and rCOJEC at 18% (95% CI, 10%–32%) ($p = 0.008$) (see Figure 3) (see flow diagram Figure 1).

Toxicity

The least treatment-related deaths were seen in patients treated with OPEC/OJEC (1.6%), compared to the St Jude NB84 protocol with 7.5% and rCOJEC with 7.1% ($p < 0.05$). There were no documented doxorubicin cardiac-related deaths in the St Jude NB84 protocol group (see flow diagram 1).

Prognostic factors

With multivariate analysis (see Table 2), statistically significant differences were demonstrated in the remission rates associated with age > 18 months ($p = 0.038$), INSS stage 4 ($p < 0.001$), ferritin > 120 ng/dl ($p < 0.001$), and unfavorable pathology according to the

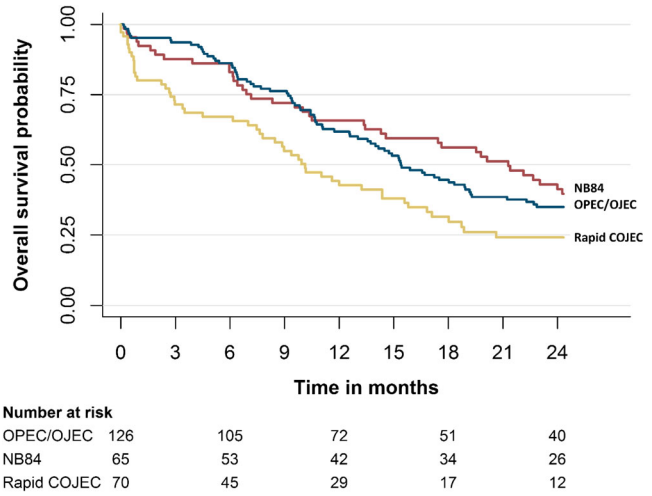

Figure 2. Kaplan-Meier curves of the two-year OS of the induction regimens ($p = 0.010$).

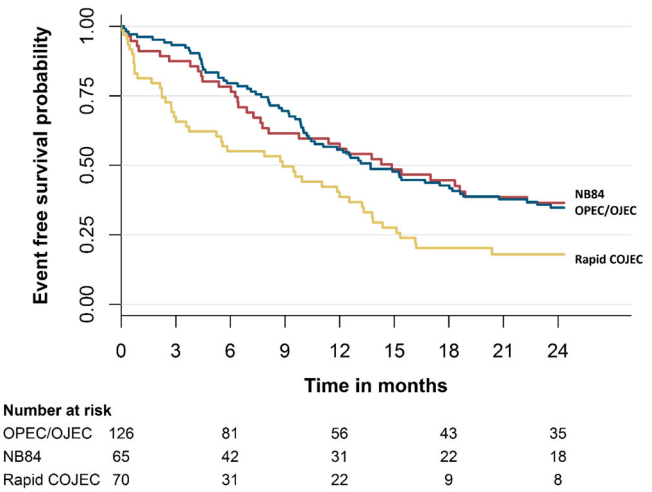

Figure 3. Kaplan-Meier curves of the two-year EFS of the induction regimens ($p = 0.008$).

International Neuroblastoma Pathology Classification (INPC) ($p = 0.023$). Nonsignificant differences were demonstrated between induction chemotherapy regimens with better remission achieved with NB84 than OPEC/OJEC ($p = 0.12$). rCOJEC had the worst outcomes ($p = 0.12$). Multivariate risk factor analysis confirmed that ferritin >120 ng/dL ($p = 0.051$) and INSS stage 4 ($p < 0.002$) were significant predictors of achieving mCR. The choice of induction chemotherapy regimen was not significant to achieve remission ($p = 0.65$). Significant prognostic factors associated with OS (see Table 4) were INSS stage 4 ($p = 0.006$) and ferritin > 120 ng/dl ($p = 0.002$), LDH >750 ($p = 0.023$) and low WFA ($p = 0.081$). The particular induction chemotherapy protocol was not shown to influence survival ($p = 0.18$). Significant prognostic factors, on univariate and multivariate analyses, associated with EFS (see Table 5) were INSS stage 4 ($p = 0.017$), ferritin > 120 ng/dl ($p < 0.001$) and the induction chemotherapy regimen ($p = 0.08$).

Table 2. Multivariate analyses with complete metastatic remission as main denominator.

	Total N (%)	Remission N (%)	No remission N (%)	*p*-Value
Sex				0.20
Male	138 (52.9%)	37/138 (26.8%)	101/138 (73.2%)	
Female	123 (47.1%)	43/123 (35.0%)	80/123 (65.0%)	
Age				0.038
0 – 18 m	51 (19.5%)	23/51 (45.1%)	28/51 (54.9%)	
18.1 m – 5 y	152 (58.2%)	43/152 (28.3%)	109/152 (71.7%)	
> 5 y	58 (22.2%)	14/58 (24.1%)	44/58 (75.9%)	
INSS				<0.001
Stage 4	223 (85.4%)	56/223 (25.1%)	167/223 (74.9%)	
Other stage	38 (14.6%)	24/38 (63.2%)	14/38 (36.8%)	
LDH				0.16
< 750	87 (33.3%)	33/87 (37.9%)	54/87 (62.1%)	
> 750	162 (62.1%)	46/162 (28.4%)	116/162 (71.6%)	
Unknown	12 (4.6%)			
Ferritin				<0.001
< 120	50 (19.2%)	27/50 (54.0%)	23/50 (46.0%)	
> 120	139 (53.3%)	36/139 (25.9%)	103/139 (74.1%)	
Unknown	72 (27.6%)			
INPC				0.023
Favorable	27 (10.3%)	15/27 (55.6%)	12/27 (44.4%)	
Unfavorable	104 (39.8%)	31/104 (29.8%)	73/104 (70.2%)	
Unknown	130 (49.8%)			
MYCN				0.37
Nonamplified	38 (14.6%)	17/38 (44.7%)	21/38 (55.3%)	
Amplified/extra copies	79 (30.3%)	27/79 (34.2%)	52/79 (65.8%)	
Unknown	144 (55.2%)			
WFA				0.47
> -1 SD	116 (44.4%)	39/116 (33.6%)	77/116 (66.4%)	
-1SD to -2 SD	41 (15.7%)	15/41 (36.6%)	26/41 (63.4%)	
< -2SD	37 (14.2%)	9/37 (24.3%)	28/37 (75.7%)	
Unknown	67 (25.7%)			
HFA				0.76
> -1 SD	97 (37.2%)	29/97 (29.9%)	68/97 (70.1%)	
-1SD to -2 SD	30 (11.5%)	11/30 (36.7%)	19/30 (63.3%)	
< -2SD	63 (24.1%)	21/63 (33.3%)	42/63 (66.7%)	
Unknown	71 (27.0%)			
Chemo regimen				0.12
St Jude NB84	65 (24.9%)	24/65 (36.9%)	41/65 (63.1%)	
OPEC/OJEC	126 (48.3%)	41/126 (32.5%)	85/126 (67.5%)	
Rapid COJEC	70 (26.8%)	15/70 (21.4%)	55/70 (78.6%)	

LDH – lactate dehydrogenase; INPC – International neuroblastoma pathology classification; INSS – International neuroblastoma staging system; WFA – weight for age (z-score); HFA – height for age (z-score); SD – standard deviations.

Nutrition

Patients with a weight for age (WFA) above the -2SD z-score had a slightly improved, though nonsignificant remission rate (>-1SD with 33.6%; -1SD to -2 SD with 36.6%) compared to wasted patients (24.3% for WFA below -2SD z-score) ($p = 0.47$). Body mass index for age and weight for height were not statistically significant as prognostic factors for survival (see Table 2).

Limitations of the study

The retrospective nature of the data limits the study because of the absence of randomization. Treatment was not standardized as regimens were based on institutional preference and disease severity. Different POUs administered similar regimens for either

Table 3. Simple and multiple logistic regression model for Remission (with multiple imputation).

	Simple logistic model		Multiple logistic model	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Sex: Female	1.47 (0.86 – 2.49)	0.16	1.36 (0.74 – 2.49)	0.33
Age[a]		0.041		0.64
18 m – 5 y	0.48 (0.25 – 0.92)	0.029	0.69 (0.32 – 1.49)	0.35
> 5 y	0.39 (0.17 – 0.88)	0.024	0.73 (0.27 – 1.99)	0.54
INSS: Stage 4	0.20 (0.09 – 0.40)	<0.001	0.26 (0.11 – 0.61)	0.002
LDH: > 750	0.62 (0.36 – 1.08)	0.095	1.12 (0.53 – 2.36)	0.76
Ferritin: > 120	0.29 (0.15 – 0.57)	<0.001	0.45 (0.20 – 1.00)	0.051
INPC: Unfavorable	0.41 (0.18 – 0.93)	0.041	0.45 (0.17 – 1.17)	0.10
MYCN: Amplified	0.75 (0.35 – 1.59)	0.46	0.72 (0.28 – 1.83)	0.49
WFA: < -2SD	0.64 (0.29 – 1.41)	0.27	0.42 (0.14 – 1.28)	0.13
HFA: < -2SD	1.11 (0.57 – 2.15)	0.77	1.52 (0.59 – 3.90)	0.38
Chemo regimen[b]		0.13 33		0.65
O/O	0.82 (0.44 – 1.54)	0.55	0.98 (0.45 – 2.13)	0.95
Rapid COJEC	0.47 (0.22 – 1.00)	0.050	0.70 (0.29 – 1.71)	0.44

[a]Reference category < 18 m.
[b]Reference category St Jude NB84.

Table 4. Simple and multiple Cox regression model for Overall survival (OS) (with multiple imputation).

	Simple Cox model		Multiple Cox model	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Sex: Female	0.63 (0.47 – 0.84)	0.002	0.67 (0.50 – 0.91)	0.011
Age[a]		0.030		0.42
18 m – 5 y	1.73 (1.15 – 2.60)	0.008	1.11 (0.71 – 1.75)	0.64
> 5 y	1.63 (1.02 – 2.60)	0.040	0.86 (0.49 – 1.51)	0.60
INSS: Stage 4	2.75 (1.70 – 4.43)	<0.001	2.11 (1.24 – 3.57)	0.006
LDH: > 750	1.87 (1.37 – 2.54)	0.001	1.51 (1.06 – 2.16)	0.023
Ferritin: > 120	2.82 (1.82 – 4.39)	<0.001	2.25 (1.35 – 3.75)	0.002
INPC: Unfavorable	1.61 (1.04 – 2.49)	0.035	1.33 (0.83 – 2.13)	0.23
MYCN: Amplified	1.19 (0.79 – 1.77)	0.41	0.97 (0.62 – 1.54)	0.91
WFA: < -2SD	1.40 (0.96 – 2.06)	0.082	1.60 (0.94 – 2.70)	0.081
HFA: < -2SD	1.16 (0.84 – 1.59)	0.37	1.13 (0.74 – 1.71)	0.57
Chemo regimen[b]		0.010		0.18
O/O	1.13 (0.79 – 1.61)	0.50	0.91 (0.60 – 1.38)	0.65
Rapid COJEC	1.75 (1.18 – 2.60)	0.005	1.28 (0.82 – 2.01)	0.28

[a]Reference category < 18 m.
[b]Reference category St Jude NB84.

curative or palliative intent. The prognosis and OS were influenced by nonstandard management indications related to surgery and radiotherapy administration. Risk stratification was limited by the availability of genetic testing especially with regard to MYCN status, deletions and mutations. The degree of supportive care differs among European, North American and South African POUs as well as between different South African POUs. The curative and palliative treatment intent differed between South African POUs with the degree of supportive care dictated by the treatment intent.

Discussion

This study compared the most commonly used induction chemotherapy protocols for HR-NB in South African POUs to identify the most effective, least toxic mCR induction

Table 5. Simple and multiple Cox regression model for Event-free survival (EFS) (with multiple imputation).

	Simple Cox model		Multiple Cox model	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Sex: Female	0.62 (0.46 – 0.85)	0.003	0.66 (0.47 – 0.92)	0.016
Age[a]		0.007		0.49
18m – 5yr	1.94 (1.21 – 3.13)	0.006	1.23 (0.72 – 2.10)	0.46
> 5y	2.31 (1.36 – 3.91)	0.002	0.99 (0.51 – 1.90)	0.97
INSS: Stage 4	2.70 (1.59 – 4.61)	<0.001	2.09 (1.14 – 3.83)	0.017
LDH: > 750	1.63 (1.18 – 2.26)	0.003	1.16 (0.79 – 1.70)	0.46
Ferritin: > 120	4.46 (2.42 – 8.24)	<0.001	3.52 (1.76 – 7.06)	<0.001
INPC: Unfavorable	1.61 (0.93 – 2.77)	0.095	1.32 (0.76 – 2.30)	0.32
MYCN: Amplified	1.12 (0.76 – 1.67)	0.57	1.02 (0.64 – 1.63)	0.92
WFA: < -2SD	1.40 (0.92 – 2.13)	0.12	1.43 (0.79 – 2.62)	0.24
HFA: < -2SD	1.24 (0.88 – 1.75)	0.22	1.22 (0.79 – 1.87)	0.38
Chemo regimen[b]		0.008		0.08
O/O	0.95 (0.65 – 1.39)	0.81	0.72 (0.46 – 1.13)	0.15
Rapid COJEC	1.66 (1.09 – 2.52)	0.018	1.10 (0.67 – 1.79)	0.70

[a]Reference category < 18 m.
[b]Reference category St Jude NB84.

chemotherapy regimen. In European studies mCR rates of 26.6–36.0% have been reported in patients treated on rCOJEC and 31.6–41.0% on OPEC/OJEC.[4,7] While the SA mCR of 32.5% on OPEC/OJEC is comparable to European studies, the mCR of 21.4% on rCOJEC is poorer than that described in European studies. The reasons were not clear, but nutritional status and available supportive care may have been different for studies in Europe.

The St Jude NB84 protocol and Memorial Sloan Kettering's (MSK) N6 protocol, doxorubicin-containing protocols from North America, achieved postinduction mCR of 77.0% ($n = 154$)[13] and 62.5% ($n = 24$),[15] respectively. The 36.9% mCR achieved in the St Jude NB84 protocol in SA is lower than remission rates in North America, but is the same as the 37% of the doxorubicin containing N5-MSKCC randomization reported during the HRNBL1.5/SIOPEN trial from 2013 to 2017.[7] The patients in the two North American studies were staged according to the Pediatric Oncology Group (POG)[13] and Children's Cancer Group (CCG).[13] The POG staging included stage B patients over the age of 12 months in the cohort,[13] while MSK staged without factoring in MYCN,[13] which was different from the SA POUs where the INRG classifications were used. The varied regional risk classifications create an unequal staging and biological profile for a standardized comparison.

The 2-year OS of the St Jude NB84 protocol (1984–1988) was 68.0%[13] while the 3-year EFS was 24.2% for patients in the OPEC/OJEC group and 31.0% for those in the rCOJEC group during European studies between 1990 and 1999.[4] More recent 2-year OS was 69.0% for rCOJEC,[7] but the protocol included an extended induction with topotecan, vincristine and doxorubicin. In our study the 2-year OS was 39.1% for the St Jude NB84 protocol, 30.7% for OPEC/OJEC and 16.3% for rCOJEC. Whereas the OPEC/OJEC outcomes compared well to the European studies, both rCOJEC and the doxorubicin-containing protocol performed worse. Although the differences in 2-year EFS of our study did not reach significance, the values were comparable to the 3-year EFS of the international studies. In a similar low- and middle income countries setting in India, doxorubicin-containing induction regimens achieved a long-term OS of 35.7% and CR of 17.6%.[16]

In North America, the treatment related mortality rate (TRM) during the St Jude protocol was reported to be 2.5%.[13] No patients were reported to have developed anthracycline-related cardiac failure.[13] Although there were no cardiac-related deaths in the SA study, the TRM was (7.5%) mainly due to myelosuppression. In Europe, the OPEC/OJEC and COJEC studies reported TRM rates of 3.2% and 4.1%,[4] respectively, whereas in the SA study they were 1.6% and 7.1%, respectively.

The doxorubicin-containing modified POG 9341 induction regimen has been used in Morocco with no toxicity-related deaths.[17] Limiting the use of doxorubicin in favor of optimizing the platinum backbone results in a superior response rate to the CCG3891 protocol, with improved intensity compared to CAdO/PE,[18] and has a more favorable acute toxicity profile than N7[19] or rCOJEC.[1]

In general, there is limited data comparing doxorubicin and nondoxorubicin containing regimens. SIOPEN randomized rCOJEC and N5-MSKCC regimens with the aim of comparing the two protocols.[7] The study concluded that rCOJEC was less toxic and no differences in postinduction remission, OS and EFS.[7] In our study, rCOJEC accounted for more toxicity-related deaths than the doxorubicin-containing St Jude NB84 protocol. OPEC/OJEC accounted for less toxicity-related deaths than both the other two protocols. The St Jude NB84 protocol had the best remission rate and 2-year OS and EFS but had a higher toxicity than OPEC/OJEC.

As in the North American studies,[13] LDH >750 U/L, ferritin >120 ng/dl, stage 4 disease and the choice of induction chemotherapy were significant prognostic denominators in the SA study. In keeping with international trends[7] and as in other middle-income countries (MIC),[20] more male patients were diagnosed with high-risk disease, yet sex was not a significant factor on multivariable analysis. HR-NB was mostly diagnosed in the 18–60 months age group, as in other LMIC,[21] and the median age of 36.1 months is higher compared to 33.2 months reported in Egypt, another MIC.[20] The greatest proportion of patients in the cohort had stage 4 disease and a larger proportion of tumors were MYCN amplified. The rate of malnutrition at diagnosis was marginally higher than in high income countries,[8] which is a cause for concern and suggests a need for more aggressive nutritional support.

The SA study reproduced the findings of both European and North American studies that various NB induction regimens were comparable to each other despite different therapeutic approaches.[4,6,7] A Cochrane review concluded that the only benefit of rCOJEC above OJEC/OPEC was the more rapid progress to autologous transplant.[4] In a MIC with limited access to transplant facilities, this benefit has little relevance. In randomized trials, rCOJEC had improved EFS compared to OPEC/OJEC through dose intensification, but was not superior to North American and other European regimens.[6]

The results of this study should be viewed in the South African context with comparisons between different HR-NB induction protocols among different centers with different supportive care guidelines, nonstandardized treatment and different treatment intents of management. The application in other countries should be evaluated according to local POUs and resources.

Conclusion

Reduction of the primary tumor size and complete remission of metastases by the end of induction chemotherapy are important prognostic factors in the treatment of NB.

With a marginal difference in outcomes with the various standard NB treatment protocols, the more favorable toxicity profile of OPEC/OJEC, especially considering malnourished children, is the most suitable induction regimen for SA. The ease of administration, favorable toxicity profile and rendering G-CSF support unnecessary are also important considerations for the future implementation of OPEC/OJEC as the standard induction regimen in HR-NB in South Africa.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, JvH. The data are not publicly available due to ethical restrictions.

Contributors' statement

Jaques van Heerden conceptualized and designed the study, collected data, performed the data analysis and wrote the manuscript. Mariana Kruger assisted with conceptualization and design of the study, supervised data analysis, critically reviewed and revised the manuscript. Kristien Wouters performed the statistical analysis. All other authors collected data in their respective pediatric oncology units and contributed significantly to the manuscript.

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Disclosure statement

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