CHEMOIMMUNOTHERAPY WITH DINUTUXIMAB BETA COMPARED TO CHEMOTHERAPY REGIMENS IN PATIENTSWITH RELAPSED/REFRACTORY NEUROBLASTOMA: SYSTEMATIC LITERATURE REVIEW AND INDIRECT TREATMENT COMPARISON

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INTRODUCTION

- Neuroblastoma is a rare cancer and the most common extracranial paediatric solid tumour, responsible for 15% of cancer deaths in children [1]. Approximately half of patients with neuroblastoma have high-risk disease, associated with the worst prognosis with respective 5-year event-free survival (EFS) and overall survival (OS) of approximately 40% and 50% [2].
- Anti-GD2 monoclonal antibodies as the standard of care for the first-line maintenance improved the survival rates in patients with high-risk neuroblastoma. In spite of potentially life-saving first-line maintenance treatment with anti-GD2 monoclonal antibodies, nearly half of the patients still relapse, and about 15% do not show sufficient response to the first line therapy [1,2].
- For many years, the initial treatment regimens for relapsed/refractory neuroblastoma included chemotherapy (CTH) combinations, usually based on temozolomide and irinotecan or topotecan. However, the synergistic combination of CTH and anti-GD2 antibodies is now becoming the therapy of choice in relapsed/refractory neuroblastoma [3]. This approach is based on the synergistic effect of chemotherapy and immunotherapy [4] and supported by evidence on continued expression of the targeted GD2 disialoganglioside in neuroblastoma tissues after relapse [5].
- Prior to availability of chemoimmunotherapy, the initial treatment regimens included chemotherapy combinations usually based on temozolomide and irinotecan or topotecan and distinct from those administered in prior treatment lines.
- Chemoimmunotherapy with anti-GD2 antibodies was first demonstrated to be effective in relasped/refractory neuroblastoma in a Children's Oncology Group randomised controlled trial ANBL1221 where dinutuximab was combined with temozolimde and irinotecan and with granulocyte-macrophage colony-stimulating factor (GM-CSF) while the control group received temozolomide, irinotecan and temsirolimus [6] .
- In 2022 a randomized controlled trial (BEACON-immuno) comparing the monoclonal anti-GD2 antibody dinutuximab beta combined with temozolomide and topotecan CTH versus CTH alone in relapsed/refractory neuroblastoma met its success criteria [7]. Even though it was the largest trial of chemoimmunotherapy (CIT) in this setting, a small number of patients enrolled (43 on CIT and 22 on CTH) calls for combining evidence from other studies of the two modalities to inform clinical practice and guide further research.

METHODS

- Studies of dinutuximab beta (DB) combined with chemotherapy and of chemotherapy alone enrolling both relapsed and refractory patients were identified in a systematic literature review using PubMed and EMBASE.
- Search terms were (relapse* OR recurren* OR refractory OR progress*) AND neuroblastoma AND (chemotherapy OR temozolomide OR temodal OR irinotecan OR topotecan OR vincristine OR doxorubicin OR cyclophosphamid* OR etoposid* OR TVD OR bevacizumab OR avastin).
- Prospective and retrospective studies reported from year 2000 till June 2024 were considered, including conference presentations, excluding letters to editor, commentaries, case reports, etc.
- Studies to be included had to be reporting relevant outcomes for minimum 10 patients and for both relapsed and refractory, as subgroup analyses were deemed not feasible due to small sample size.
- Studies including other solid tumours were excluded if not reporting separately on neuroblastoma.
- The following treatment combinations were considered for inclusion: temozolomide plus irinotecan (TEMIRI), temozolomide plus topotecan (TOTEM), cyclophosphamide plus topotecan (TOPO/CTX), with and without DB and with and without bevacizumab (BEV).
- Studies were considered for inclusion also with additional treatment that was not a CTH.
- For inclusion, the minimum required cohort size was N=10 and outcome measures of interest were Objective Response Rate (ORR, measured as best response rate consistently with the BEACON-immuno trial) and either progression-free survival (PFS) or EFS. As 12 of the 22 patients in the chemotherapy arm of the BEACON-immuno trial, cross-over to the chemoimmunotherapy arm, overall survival was not included in this study.
- Publications were reviewed independently by two authors, with the third author resolving any disagreements regarding inclusion.
- Guyot 2012 algorithm [8] was implemented in R (ver. 4.3.2) with survminer and survival packages, and Digitizelt software were used for digitisation of Progression Free Survival (PFS) Kaplan-Meier curves with approximated individual patient data pooled for analyses using log-rank test and Cox proportional hazards model with no adjustments. Objective response rates (ORR) measured as best response were compared using relative risk (RR) and odds ratio (OR).
- Number Needed to Treat (NNT) was calculated for PFS at 24 months and for ORR.

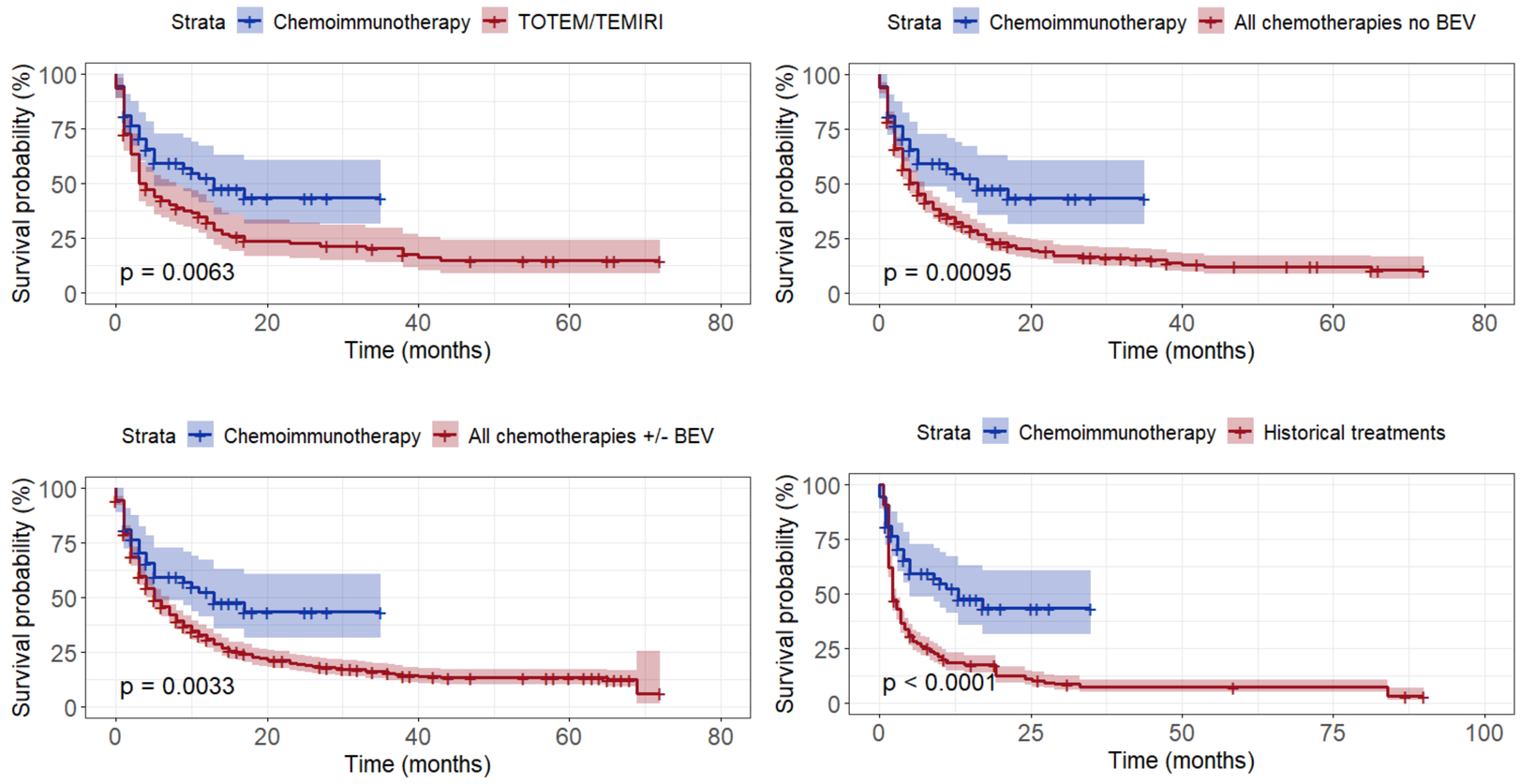

Figure 1. Pooled Kaplan-Meier curves for Progression-Free Survival on chemoimmunotherapy compared to four different sets of chemotherapy data. A. TOTEM/TEMIRI only. B. All chemotherapies without bevacizumab. C. All chemotherapies with or without bevacizumab. D. Historical treatments from early stage clinical trials, including treatments other than chemotherapy. P-values are shown for log-rank test.

RESULTS

- The literature review identified 2,329 publications with 358 remaing when filters were applied.
- Fifteen studies with 636 patients were included in the review. Three studies were randomised controlled trials with one involving CIT with dinutuximab beta.
- One study was an individual patient data meta-analysis of three studies with various CTH regimens.
- One additional publicaition reporting on historical experience with multiple early phase treatments was identified, but not included in the review due to incomplete information on treatments and lack of ORR data (London 2017). This data was still used a comparator to CIT as one of the scenarios.
- The studies used 20 treatment arms: three arms for CIT and 17 arms for CTH.
- TOTEM regimen was used in four arms, TEMIRI in six, TopoCycle in three, and temozolomide alone in four.
- In five CTH arms an additional treatment was given: temsirolimus in one, alisertib in one, nifurtimox in one, and BEV in four.
- In Scenario A, CIT with DB combined with CTH compared to TOTEM or TEMIRI CTH arms (not including BEV arms) improved PFS with HR=0.58 [95%CI: 0.39-0.86], p=0.007). RR for ORR was 3.02 [2.01-4.53], p<0.001 and OR was 4.99 [2.77-9.00], p<0.001. NNT was 5 for PFS and 4 for ORR.
- In Scenario B, CIT with DB compared to all CTH arms without bevacizumab improved PFS with HR=0.55 [0.39-0.79], p=0.001). RR was 2.60 [1.95-3.46], p<0.001, OR was 4.16 [2.56-6.74], p<0.001. NNT was 4 for PFS and ORR.
- In Scenario C, CIT with DB improved PFS versus all chemotherapy arms with or without BEV: HR=0.59 [0.42-0.85], p=0.004). RR was 2.54 [1.93-3.33], p<0.001, and OR was 4.04 [2.52-6.46], p<0.001. NNT was 5 for PFS and 4 for ORR.
- In the additional Scenario D, CIT with DB improved PFS versus historical treatents in early phase clinical trials: HR=0.42 [0.30-0.61], p<0.001. NNT (PFS) was 4.

Table 1. Characteristics of studies included in the analyses

Source Study	Regimen used	N	EFS/PFS	ORR	% Relapsed	%MYCN-A****	Age at enrolment (y)	Previous anti-GD2
Moreno 2024 [9]	T	36	PFS KM	17.5%	58.8%	20.5%	5	40%
	IT (TEMIRI)	30	PFS KM					
	TTo (TOTEM)	14	PFS KM					
	BT	34	PFS KM	26.3%	57.5%	25.6%	5	40%
	BIT	30	PFS KM					
	BTTo	16	PFS KM					
Eslin 2023 [10]	TOPO/CTX+nifurtimox	43	EFS KM	16.3%	N/R	37.8%	7.1	
Wieczorek 2023 [11]	DB+chemo	25	PFS KM	64.0%	80%	47.8%	2.8 (at diagn.)	56%
Olgun 2022 [12]	DB+chemo	19	N/R	63.2%	53%	17.7%	5.5	5.3%
Gray 2022 [13]	DB+chemo	43	PFS KM	34.9%	44%	30.2%	5	41.9%
Gray 2022 [13]	TOTEM	22	PFS KM	18.2%	55%	27.3%	5	27.3%
DuBois 2018 [14]	TEMIRI+alisertib	32	PFS KM	15.65	N/R	31.0%	7.8	N/R
Mody 2017 [15]	TEMIRI+temsirolimus	18	PFS KM	5.6%	56%	27.8%	7	22.2%
Modak 2017 [16]	BIT	33	PFS KM	9.1%	70%	15.2%	6.4	N/R
DiGiannatale 2014 [17]	TOTEM, T***	38	PFS KM	23.7%	66%	30.3%	5.4	N/R
Bagatell 2011 [18]	TEMIRI	55	EFS KM	14.6%	73%	32.4%	3.6	N/R
London 2010 [19]	TOPO/CTX	57	PFS KM	31.6%	N/R	N/R	5.1	N/R
Rubie 2006 [20]	T	25	PFS KM	28.0%	60%	36.0%	6.5	N/R
De Sio 2006 [21]	T	17	N/R	5.9%	N/R	N/R	N/R	N/R
Saylors 2001 [22]	TOPO/CTX	13	N/R	46.2%	N/R	N/R	N/R	N/R
Moreno 2016 [23]*	T, TOTEM, TVD	71	PFS KM	29.6%	66%	34.4%	N/R	N/R
London 2017 [24]**	Various therapies	383	PFS KM	N/R	N/R	16.4%	N/R	N/R

*Meta-analysis of three identified studies, used instead of individual studies
** Study of a early stage clinical trial data including chemotherapy, but with insufficent reporting for inclusion in the systematic review. Used as comparator in Scenario 4.
***For temozolomide data from Rubie 2006 reported.
****As percentage of patients with known MYCN status

EFS = Event Free Survival
PFS = Progression Free Survival
ORR = Objective Response Rate
MYCN-a = MYCN-Amplified

T = temozolomide
IT = TEMIRI = irinotecan + temozolomide
TTo = TOTEM = topotecan + temozolomide
BIT = bevacizumab + irinotecan + temozolomide
BTTo = bevacizumab + temozolomide +topotecan
TOPO/CTX = topotecan + cyclophosphamide
TVD = topotecan + vincristine + doxorubicin

Table 2. Scenario results

Outcome	Scenario A	Scenario B	Scenario C	Scenario D
Comparator arm	TOTEM/ TEMIRI	CTX without B	CTX +/- B	COG clinical trials
EFS/PFS HR	0.58	0.55	0.59	0.42
95% CIs	0.39-0.86	0.39-0.79	0.42-0.85	0.30-0.61
P-value	0.007	0.001	0.004	p<0.001
EFS/PFS NNT	5	4	5	4
ORR RR	3.02	2.60	2.54	-
95% CIs	2.01-4.53	1.95-3.46	1.93-3.33	-
P-value	p<0.001	p<0.001	p<0.001	-
ORR OR	4.99	4.16	4.04	-
95% CIs	2.77-9.00	2.56-6.74	2.52-6.46	-
P-value	p<0.001	p<0.001	p<0.001	-
ORR NNT	4	4	4	-

EFS = Event Free Survival
PFS = Progression Free Survival
ORR = Objective Response Rate
NNT = Number Needed to Treat
CTX = Chemotherapy
B = Bevacizumab
RR = Relative Risk
OR = Odds Ratio

CONCLUSIONS

- Our results demonstrate improved objective response and progression free survival outcomes with dinutuximab beta chemoimmunotherapy in relapsed/refractory neuroblastoma and support recommendations for its use in this setting.
- Analysis with individual patient data adjusted for predictors of outcomes would allow for a more precise estimate of treatment effect.

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DISCLOSURE

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