Original Article

Efficacy of post-induction therapy for high-risk neuroblastoma patients with end-induction residual disease

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BACKGROUND: High-risk neuroblastoma patients with end-induction residual disease commonly receive post-induction therapy in an effort to increase survival by improving the response before autologous stem cell transplantation (ASCT). The authors conducted a multicenter, retrospective study to investigate the efficacy of this approach. **METHODS:** Patients diagnosed between 2008 and 2018 without progressive disease with a partial response or worse at end-induction were stratified according to the post-induction treatment: 1) no additional therapy before ASCT (cohort 1), 2) post-induction "bridge" therapy before ASCT (cohort 2), and 3) post-induction therapy without ASCT (cohort 3). χ^2 tests were used to compare patient characteristics. Three-year event-free survival (EFS) and overall survival (OS) were estimated by the Kaplan-Meier method and survival curves were compared by log-rank test. **RESULTS:** The study cohort consisted of 201 patients: cohort 1 (n = 123), cohort 2 (n = 51), and cohort 3 (n = 27). Although the end-induction response was better for cohort 1 than cohorts 2 and 3, the outcomes for cohorts 1 and 2 were not significantly different ($P = .77$ for EFS and $P = .85$ for OS). Inferior outcomes were observed for cohort 3 ($P < .001$ for EFS and $P = .06$ for OS). Among patients with end-induction stable metastatic disease, 3-year EFS was significantly improved for cohort 2 versus cohort 1 ($P = .04$). Cohort 3 patients with a complete response at metastatic sites after post-induction therapy had significantly better 3-year EFS than those with residual metastatic disease ($P = .01$). **CONCLUSIONS:** Prospective studies to confirm the benefits of bridge treatment and the prognostic significance of metastatic response observed in this study are warranted. ***Cancer* 2022;128:2967-2977**. © *2022 American Cancer Society*.

KEYWORDS: autologous transplantation, neuroblastoma, prognosis, survival, treatment response.

INTRODUCTION

Approximately half of all patients diagnosed with neuroblastoma have aggressive, high-risk disease.[1-3] Increasingly intensive multimodality approaches have led to improved survival,[4,5] and significantly increased event-free survival (EFS) has been observed with tandem cycles of high-dose therapy and autologous stem cell transplantation (ASCT) in comparison with a single transplant.[6] However, approximately 40% of high-risk patients continue to relapse, and survival for this cohort is dismal.[7,8] Although outcomes are better for patients with refractory neuroblastoma,[9,10] long-term survival remains poor.[11,12] Significantly inferior EFS was reported for patients enrolled in the Children's Oncology Group (COG) A3973 high-risk clinical trial with post-induction meta-iodobenzylguanidine (MIBG) Curie scores of >2 versus ≤2.[12] Similarly, among patients enrolled in the International Society of Paediatric Oncology European Neuroblastoma Group (SIOPEN) HR-NBL1 high-risk trial, worse EFS was associated with post-induction SIOPEN MIBG skeletal scores of >3 versus ≤3.[13] Furthermore, less than a partial response (PR) at end-induction was associated with significantly worse EFS and overall survival (OS) for patients enrolled in 4 consecutive high-risk COG trials.[11]

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On the basis of these observations, we and others have hypothesized that the survival of high-risk patients with residual disease at end-induction will be enhanced if the disease burden can be reduced with "bridge" therapy before consolidation with ASCT. Many providers are currently treating individual patients with end-induction residual disease with regimens shown to have anti-neuroblastoma activity in early-phase clinical trials, including dinutuximab combined with irinotecan and temozolomide (DIT),[14,15] radiolabeled MIBG (^{131}I-MIBG),[16] and combinations of chemotherapeutic agents.[17,18] However, questions remain regarding the benefits of this approach and whether a response to bridge therapy is associated with survival. To address these questions, we conducted a multicenter, retrospective study of high-risk neuroblastoma patients with end-induction residual disease and analyzed treatment approaches, responses to post-induction therapy, and patient outcomes.

MATERIALS AND METHODS

High-risk neuroblastoma patients without progressive disease (PD) who were diagnosed between January 1, 2008, and December 31, 2018, with a PR or worse at end-induction were identified at the University of Chicago Comer Children's Hospital, the Children's Hospital of Philadelphia, the Ann & Robert H. Lurie Children's Hospital of Chicago, Seattle Children's Hospital, the University of Michigan, and Texas Children's Hospital. Patient and tumor characteristics,[1] treatments, and outcome data were abstracted from electronic medical records. The patients were classified as high-risk on the basis of the 2006 COG risk criteria.[3,19] Responses to induction, bridge, and post-induction treatments were determined according to the 2017 International Neuroblastoma Response Criteria (INRC)[20] with a modification for the small number of patients who did not undergo a bone marrow evaluation at these time points (end-induction, n = 8; post-bridge treatment, n = 1; and post-induction treatment, n = 1). In those cases, the overall response was determined on the basis of primary tumor and metastatic soft tissue and bone disease responses. In separate analyses, we evaluated the metastatic response in International Neuroblastoma Staging System stage 4 patients according to the INRC for metastatic soft tissue and/or bone (component 1) and bone marrow (component 2).[20] A metastatic complete response (CR) was defined as a CR in both components; a metastatic PR was defined as a PR in component 1 and a CR, a PR, or minimal disease in component 2; and metastatic stable disease (SD) was defined as SD in at least 1 component and no component with PD. The metastatic response for 10 patients with an unknown bone marrow response was defined by the response in component 1.

The study was approved by the institutional review boards at the University of Chicago, the primary study site, and each of the collaborating institutions according to the US Common Rule ethical guidelines. Written informed consent was obtained for patients according to local institutional review board requirements (eg, patients requiring prospective data collection).

Study Design

Eligibility for this retrospective, multi-institutional study was restricted to patients with a PR or worse at end-induction. The INRC response was confirmed by computed tomography or magnetic resonance imaging, bone marrow studies, and MIBG scan.[20] For patients with MIBG-nonavid tumors, the extent of disease was evaluated with [18F]-fluorodeoxyglucose/positron emission tomography scans.[21] MIBG scans performed at Seattle Children's Hospital were reviewed by radiologists at the University of Chicago for the Curie score calculation. All other institutions calculated Curie scores locally. Investigators at each institution underwent virtual training to facilitate harmonized data abstraction, disease status criteria, and REDCap data entry. Patients were stratified into 1 of 3 cohorts according to the treatment that they received after induction therapy. Treatment was based on physician, institutional, or family preferences. Clinicians from each institution were surveyed to evaluate how end-induction Curie scores and bone marrow disease influenced their current treatment strategies.

Statistical Methods

χ^2 tests were used to compare patient characteristics and treatment responses according to cohorts. The Mann-Whitney *U* test with Benjamini-Hochberg correction for multiple testing was used to compare the year of diagnosis between treatment groups and Curie scores among patients at different time points during therapy. Three-year EFS (the time from diagnosis to the last follow-up encounter, relapse, or death) and OS (the time from diagnosis to the last follow-up or death) were estimated with the Kaplan-Meier method,[22] and survival curves were compared with the log-rank test.[23] Differences in EFS and OS between patient cohorts were analyzed with Cox proportional hazards models. The proportional hazards assumption was validated for all models. Models were not constructed for analyses of subgroups within a cohort

because of small sample sizes. Statistical analyses were performed with Stata 16.1, R 3.6.0, and Prism 9.1.2.

RESULTS

Patient Characteristics and Treatments

The entire cohort consisted of 201 high-risk neuroblastoma patients with a PR or worse at end-induction. The patients were categorized into different cohorts based on the post-induction treatment received. Cohort 1 (n = 123) underwent consolidation with ASCT directly after the completion of induction therapy. Cohort 2 (n = 51) received bridge therapy before ASCT, and cohort 3 (n = 27) received post-induction therapy but did not undergo ASCT (Fig. 1A). The cohort profile according to the end-induction INRC response is detailed in Figure 1B. Post-induction treatment changed over time, and significantly more patients received DIT in recent years in comparison with ^{131}I-MIBG ($P < .001$; Supporting Fig. 1). All clinicians currently consider bridge or post-induction therapy for patients with end-induction metastatic disease and Curie scores of >5 or bone marrow with >10% tumor cells. Bridge or post-induction therapy is also considered by >50% of the clinicians for patients with end-induction metastatic disease and Curie scores of >2 but ≤5; a reduction in the Curie score of <50%, regardless of the absolute score; or bone marrow with >5% but ≤10% tumor cells. In cohort 3, the decision to not consolidate with ASCT was based on a poor metastatic response to post-induction therapy. For 3 of the 6 patients who achieved a metastatic CR, the decision to not proceed with ASCT was made by family members.

Patient clinical features and tumor biomarkers[3] are summarized in Table 1. Although all patients were high-risk,[19] cohorts 2 and 3 had a higher proportion of patients with an unfavorable age (≥18 months old)[24] and stage (International Neuroblastoma Staging System stage 4)[6] in comparison with cohort 1. In contrast, among patients with a known *MYCN* status, *MYCN* amplification, an unfavorable genomic biomarker,[25] was identified in a higher percentage of patients in cohort 1 versus cohorts 2 and 3.

Responses to Induction Therapy Differed According to the Cohort

The end-induction response differed significantly among the cohorts ($P < .001$; Table 2), with a higher

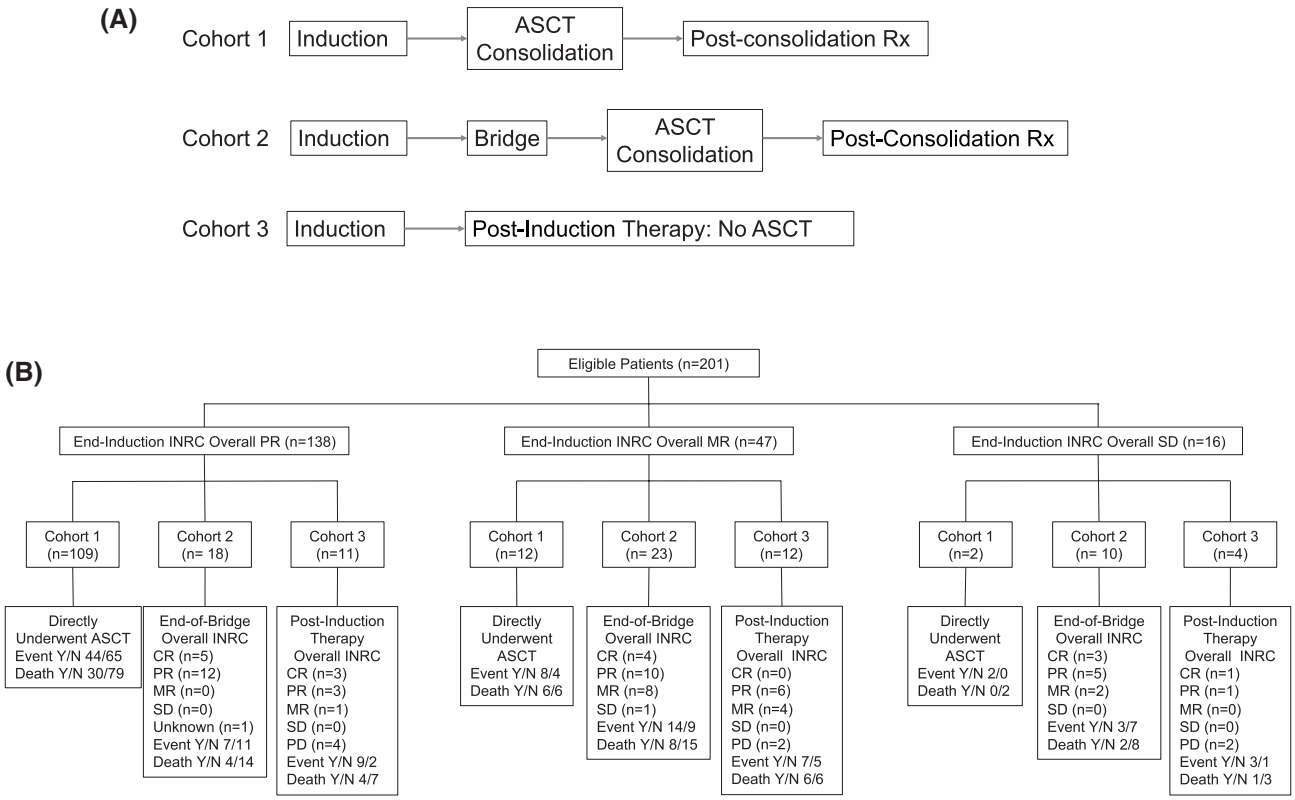


FIGURE 1. (A) Schematic of the treatment cohorts and (B) cohort profile according to the end-induction overall INRC response. ASCT indicates autologous stem cell transplantation; CR, complete response; INRC, International Neuroblastoma Response Criteria; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 1. Patient and Tumor Characteristics According to the Treatment Cohort

	Cohort 1 (n = 123), No. (%)	Cohort 2 (n = 51), No. (%)	Cohort 3 (n = 27), No. (%)	*P*
Age at diagnosis				
<18 mo	26 (21.5)	3 (5.9)	0 (0)	.002
≥18 mo	95 (78.5)	48 (94.1)	27 (100)	
Unknown	2	0	0	
Sex				
Male	81 (65.8)	31 (60.8)	11 (40.7)	.053
Female	42 (34.2)	20 (39.2)	16 (59.3)	
INSS stage				
4	110 (89.4)	51 (100)	27 (100)	.028
3	12 (9.8)	0 (0)	0 (0)	
2b	1 (0.8)	0 (0)	0 (0)	
MYCN status				
Nonamplified	63 (58.9)	32 (72.7)	23 (88.5)	.008
Amplified	44 (41.1)	12 (27.3)	3 (11.5)	
Unknown	16	7	1	
Histology				
Favorable	6 (5.9)	1 (2.4)	3 (13.0)	.23
Unfavorable	95 (94.1)	40 (97.6)	20 (87.0)	
Unknown	22	10	4	
Ploidy				.77
Hyperdiploid	34 (58.6)	13 (59.1)	9 (69.2)	
Diploid	24 (41.4)	9 (40.9)	4 (30.8)	
Unknown	65	29	14	
No. of ASCTs				.81[a]
1	80 (65)	33 (64.7)	0	
2	42 (34.2)	18 (35.3)	0	
>2	1 (0.8)	0 (0)	0	

Abbreviations: ASCT, autologous stem cell transplantation; INSS, International Neuroblastoma Staging System.
[a]The *P* value was calculated for cohort 1 versus cohort 2.

proportion of cohort 1 patients achieving a better overall response in comparison with cohorts 2 and 3. The metastatic response at end-induction was also better in cohort 1. Only 3.2% of cohort 1 patients had end-induction SD in metastatic soft tissue and bone, whereas 51% and 48.2% did so in cohorts 2 and 3, respectively. Similarly, bone marrow SD at end-induction was detected in only 7.4% of cohort 1 patients but in 33.3% and 18.5% of cohort 2 and cohort 3 patients, respectively. Furthermore, the median end-induction Curie score was significantly lower in cohort 1 versus cohort 2 ($P < .001$; Supporting Fig. 2).

Survival According to the Cohort

For cohort 1, 3-year EFS and OS were 58.9% (95% CI, 49.2%-67.4%) and 80.2% (95% CI, 71.7%-86.4%), respectively (Fig. 2A,B). Although the proportion of patients with a poor end-induction response was higher in cohort 2 versus cohort 1, EFS and OS were not significantly different ($P = .77$ for EFS and $P = .85$ for OS). EFS, but not OS, was significantly inferior for cohort 3 versus cohorts 1 and 2 ($P < .001$ for EFS and $P = .06$ for OS). After accounting for stage and *MYCN* status, significantly inferior EFS (adjusted hazard ratio, 0.32; 95% CI, 0.19-0.54; $P < .001$) and OS (adjusted hazard ratio, 0.49; 95% CI, 0.25-0.98; $P < .042$) were observed for cohort 3 patients in comparison with cohorts 1 and 2. The median follow-up time for all patients was 44 months (interquartile range [IQR], 25-74 months) with median follow-up times of 50 months (IQR, 25-84 months), 43 months (IQR, 29-60 months), and 29 months (IQR, 16-64 months) for cohorts 1, 2, and 3, respectively.

Outcomes of Stage 4 Patients in Cohort 1 According to the End-Induction Metastatic Response

At end-induction, 28 (25.5%) of the 110 stage 4 patients in cohort 1 met the INRC for a CR at metastatic sites. Bone marrow involvement was not detected at diagnosis or at end-induction in 38 patients (34.5%). Significantly worse EFS was observed among the 82 patients (74.5%) with end-induction metastatic disease in comparison with those without end-induction metastatic disease ($P = .02$; Fig. 2C). However, OS did not significantly differ ($P = .27$; Fig. 2D).

Treatments, Responses, and Outcomes of Cohort 2 Patients

The bridge treatment regimens that cohort 2 patients received are shown in Tables 3 and 4. Of the 51 patients, 44 (86.3%) received therapies that included DIT and/or ^{131}I-MIBG. Six patients were treated with combination

TABLE 2. 2017 INRC Responses of Primary Tumors, Soft Tissue and Bone Metastases, and Bone Marrow and Overall Responses

	Cohort 1 (n = 123) No. (%)	Cohort 2 (n = 51) No. (%)	Cohort 3 (n = 27) No. (%)	*P*
End-induction primary tumor response				
CR	54 (43.9)	25 (49.0)	11 (40.7)	.001
PR	66 (53.7)	15 (29.4)	11 (40.7)	
SD	2 (1.6)	8 (15.7)	5 (18.6)	
Not evaluable[a]	1 (0.8)	1 (2.0)	0 (0)	
Unknown response[b]	0 (0)	2 (3.9)	0 (0)	
End-induction metastatic soft tissue and bone disease response				
CR	37 (30.1)	3 (5.9)	4 (14.8)	<.001
PR	68 (55.3)	21 (41.2)	10 (37.0)	
SD	4 (3.2)	26 (51.0)	13 (48.2)	
Not evaluable[a]	14 (11.4)	1 (1.9)	0 (0)	
Unknown response[b]	0 (0)	0 (0)	0 (0)	
End-induction bone marrow metastasis response				
CR	41 (33.3)	14 (27.5)	7 (25.9)	<.001
MD	33 (26.0)	9 (17.7)	8 (29.6)	
SD	9 (7.4)	17 (33.3)	5 (18.5)	
Not evaluable[a]	41 (33.3)	5 (9.8)	5 (18.5)	
Unknown response[b]	0 (0)	6 (11.8)	2 (7.4)	
End-induction overall INRC disease response[c]				
PR	109 (88.6)	18 (35.3)	11 (40.8)	<.001
MR	12 (9.8)	23 (45.1)	12 (44.4)	
SD	2 (1.6)	10 (19.6)	4 (14.8)	

Abbreviations: CR, complete response; INRC, International Neuroblastoma Response Criteria; MD, minimal disease; MR, minor response; PR, partial response; SD, stable disease.
[a]The response was not evaluable: The site was not involved at diagnosis and remained uninvolved.
[b]Unknown response of evaluable disease: The required imaging or bone marrow evaluation was not performed.
[c]The overall INRC response was determined with 2 components if a bone marrow evaluation was not performed.

chemotherapy with or without surgery and radiation, and 1 patient received radiation alone. The response to bridge therapy was determined from end-induction to end-of-bridge therapy. An overall CR after bridge therapy was observed in 12 patients (23.5%) who received DIT alone (n = 7), DIT plus chemotherapy (n = 1) or ^{131}I-MIBG (n = 1), ^{131}I-MIBG alone (n = 1), multi-agent chemotherapy (n = 1), or chemotherapy plus cixutumumab (n = 1; Table 3). Sixteen patients (30.8%) with either a minor response or SD at end-induction improved to a PR. Significantly improved EFS was observed for patients who achieved an overall CR after bridge therapy ($P = .03$; Fig. 2E). The overall response to bridge treatment was not associated with OS ($P = .13$; Fig. 2F). In a separate analysis, the EFS of cohort 2 patients who achieved a metastatic CR at end-of-bridge therapy was compared with the EFS of those who did not. A trend of improved EFS was observed among patients with a metastatic CR at end-of-bridge, but statistical significance was not reached (3-year EFS, 73.8% [95% CI, 38.5%-90.8%] vs 46.5% [95% CI, 29.1%-62.2%]; log-rank $P = .1$; Fig. 2G). No difference in OS was seen (3-year OS, 100% vs 81.4% [95% CI, 62.9%-91.2%]; log-rank $P = .44$; Fig. 2H).

Outcomes of Cohort 1 and 2 Patients With Metastatic Disease at End-Induction

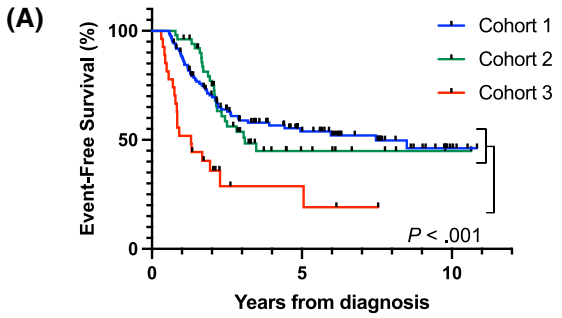
Metastatic disease was detected at end-induction in 82 stage 4 patients in cohort 1 (74.5%) and in 49 patients in cohort 2 (96.1%). Among those with SD at metastatic sites at end-induction, significantly improved EFS was observed for cohort 2 versus cohort 1 ($P = .04$; Fig. 3A). OS was not significantly different ($P = .56$; Fig. 3B). Among cohort 1 and 2 patients who achieved a metastatic PR at end-induction, there was no significant difference in EFS at 3 years (EFS, 52% [95% CI, 39%-63.5%] vs 44% [95% CI, 19.2%-66.5%]; log-rank $P = .9$) or OS at 3 years (OS, 75.1% [95% CI, 62.4%-84%] vs 69.2% [95% CI, 40.4%-86.1%]; log-rank $P = .8$).

Treatments, Responses, and Outcomes of Cohort 3 Patients

The post-induction treatments that cohort 3 patients received are summarized in Supporting Table 1. More than 70% of the patients were treated with regimens that included DIT and/or ^{131}I-MIBG. For 10 (37%) of the 27 patients, the overall INRC disease response improved from end-induction with post-induction therapy. A total of 4 patients achieved an overall CR with post-induction therapy; they included 3 patients who received DIT as part of their post-induction therapy and 1 patient who was treated with a combination therapy that included ^{131}I-MIBG. Of the 23 patients with residual metastatic disease at end-induction, 6 achieved a metastatic CR with post-induction therapy, and these patients had significantly improved 3-year EFS in comparison with those with residual metastatic disease ($P = .01$). A trend of improved OS for patients who achieved a metastatic CR was observed, although statistical significance was not reached ($P = .057$).

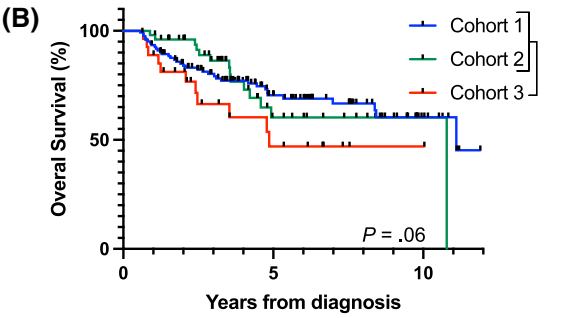
DISCUSSION

In this retrospective study, the treatment for high-risk neuroblastoma patients with end-induction residual disease varied widely and was largely based on their



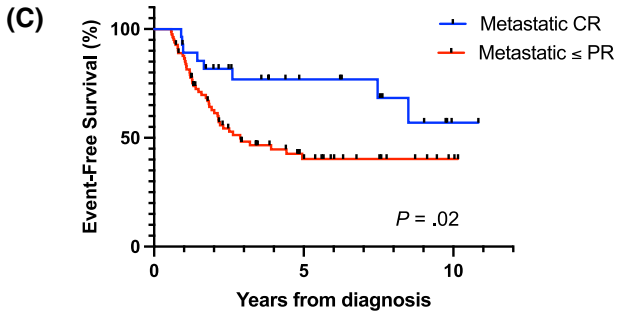
Number at Risk

Cohort 1	123	36	4
Cohort 2	51	8	1
Cohort 3	27	3	0



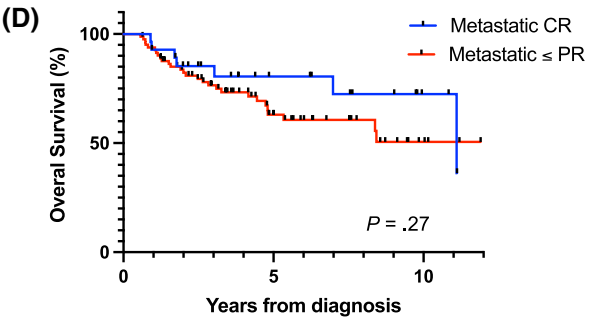
Number at Risk

Cohort 1	123	47	8
Cohort 2	51	12	2
Cohort 3	27	2	1



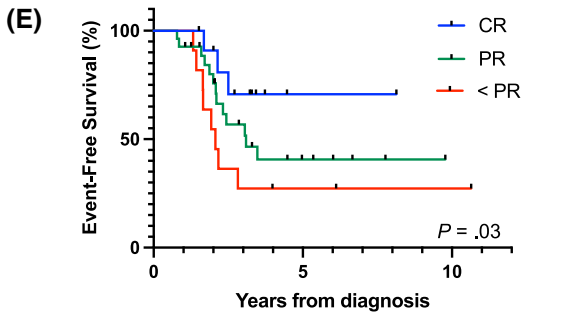
Number at Risk

Metastatic CR	28	11	1
Metastatic ≤ PR	82	17	2



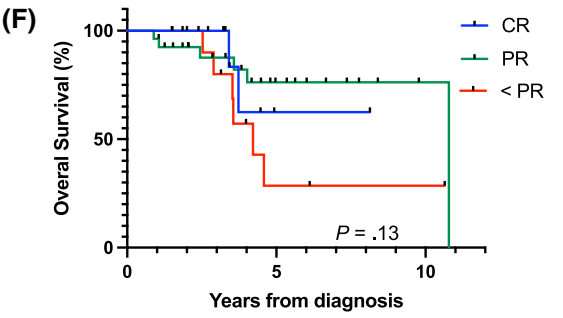
Number at Risk

Metastatic CR	28	12	3
Metastatic ≤ PR	82	27	4



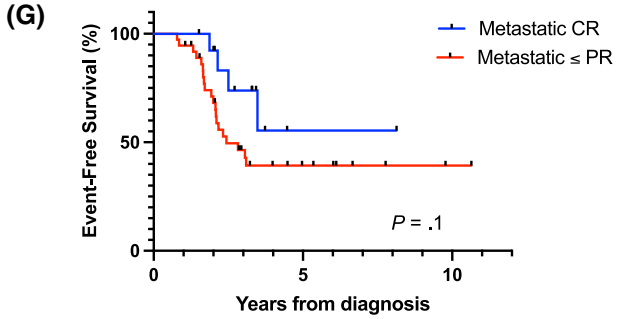
Number at Risk

CR	12	1	0
PR	27	6	0
< PR	11	2	1



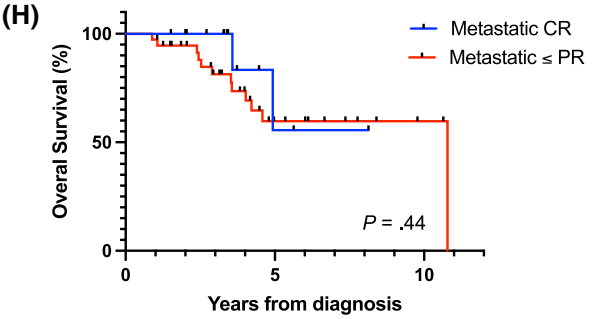
Number at Risk

CR	12	1	0
PR	27	9	1
< PR	11	2	1



Number at Risk

Metastatic CR	14	1	0
Metastatic ≤ PR	37	7	1



Number at Risk

Metastatic CR	14	2	0
Metastatic ≤ PR	37	10	2

FIGURE 2. Probability of (A) EFS and (B) OS for patients according to the treatment cohort, (C) EFS and (D) OS for stage 4 patients in cohort 1 with and without an end-induction metastatic CR, (E) EFS and (F) OS for patients in cohort 2 according to the overall INRC response at end-of-bridge therapy, and (G) EFS and (H) OS for patients in cohort 2 with and without a metastatic CR at end-of-bridge therapy. CR indicates complete response; EFS, event-free survival; INRC, International Neuroblastoma Response Criteria; OS, overall survival; PR, partial response.

responses at metastatic sites. Thus, the percentage of cohort 1 patients with residual metastatic disease at end-induction was less than that for cohorts 2 and 3. Despite these differences in end-induction responses, EFS and OS did not significantly differ for cohorts 1 and 2, and this suggests that patients in cohort 2 may have benefited from the bridge therapy. Among patients with end-induction stable metastatic disease, EFS was significantly improved for cohort 2 versus cohort 1, and this further supports the efficacy of bridge treatment. Although no difference in OS was observed, this may reflect the effects of additional treatments that these patients may have received to treat relapsed disease.[14,26,27] We did not detect differences in EFS for cohort 1 and 2 patients with an end-induction metastatic PR. The disease burden can vary significantly among patients classified as having a metastatic PR, and larger cohorts will need to be studied to determine whether the effects of bridge therapy differ among patients with more versus less extensive metastatic disease and/or specific disease sites. We recognize that this study has potential sources of bias, including a lead time for cohort 2 patients, as these patients underwent ASCT after receiving bridge treatments. Although the average number of cycles of bridge treatment was 3, which indicated that the lead time was approximately 2 months for most cohort 2 patients, future studies will be needed to confirm the efficacy of bridge therapy.

Our results also indicate that the presence of metastatic disease before ASCT is associated with inferior EFS. Cohort 1 patients with refractory metastatic disease at end-induction had significantly worse EFS than patients with only residual disease at the primary tumor site. A trend associating residual metastatic neuroblastoma at end-of-bridge therapy with inferior EFS was also observed in cohort 2 patients, but statistical significance was not reached, likely because of the small number of patients analyzed. The prognostic strength of end-induction metastatic disease highlights the limitation of studies evaluating the impact of the extent of primary surgical resection on survival. Differences in metastatic responses among the study cohorts likely contributed to the conflicting results and ongoing debate about the clinical value of nearly complete gross resection of the primary tumor.[28-31]

Cohort 3 patients had inferior EFS and OS in comparison with cohorts 1 and 2. Ten patients (37%) developed PD while receiving post-induction therapy, and 6 (22%) had no improvement in their disease response. On the basis of their poor response to post-induction therapy, these patients did not undergo consolidation with ASCT. Interestingly, 6 patients who achieved a metastatic CR with post-induction therapy also did not undergo ASCT, and all remained alive. Favorable outcomes have also been reported for patients with a CR at end-induction treated with anti-disialoganglioside (GD2) monoclonal antibodies without ASCT in a single-institution study.[32] High-dose therapy with ASCT is known to be associated with acute toxicities and late effects that negatively affect the long-term health of children with high-risk neuroblastoma,[33,34] and this highlights the need for novel biomarkers to identify patients who may not require ASCT to achieve long-term survival.

Bridge therapy was previously evaluated in the prospective, phase 3 SIOPEN HR-NBL1 study. In that trial, only patients with a metastatic CR or PR limited to ^{123}I-MIBG uptake in 3 abnormal skeletal areas on scintigraphy and with no bone marrow disease were eligible to proceed to consolidation with high-dose therapy and ASCT.[5] Patients who did not achieve this response received 2 courses of post-induction therapy consisting of topotecan, vincristine, and doxorubicin.[35] However, in contrast to our results, the 23 patients who responded to bridge therapy and underwent ASCT had significantly lower 5-year EFS in comparison with those who did not require this treatment.[5] These conflicting results may reflect the differences in the patient cohorts due to the clinical trial eligibility criteria as well as the disparate bridge regimens.

The results of this retrospective study suggest that bridge treatments that include DIT and/or ^{131}I-MIBG before ASCT significantly improve the EFS of high-risk patients with SD in metastatic sites. Prospective clinical trials will be needed to validate these findings and identify those patients most likely to benefit from bridge therapy. Additional studies to confirm the favorable outcomes that we observed among patients who achieved a metastatic CR with post-induction therapy without ASCT are also warranted.

TABLE 3. Cohort 2 Bridge Therapy and Disease Response From End-Induction to End-of-Bridge Therapy

Bridge Therapy	No. of Patients	No. of Bridge Treatment Cycles	End-Induction Overall INRC Response, No.	End-of-Bridge Overall INRC Response, No.	End-of-Bridge Primary Tumor Response, No.	End-of-Bridge Metastatic Bone and Soft Tissue Response, No.	End-of-Bridge Bone Marrow Response, No.	Event: Y/N	Death: Y/N
DIT alone	20	1-6	CR: 0 PR: 7 MR: 10 SD: 3	CR: 7 PR: 10 MR: 3 SD: 0	CR: 13 PR: 4 SD: 2 NE 1[a] Unknown: 0[b]	CR: 8 PR: 11 SD: 1 NE: 0[a] Unknown: 0[b]	CR: 17 PR: 2 MD: 0 SD: 0 NE: 1[a] Unknown: 0[b]	7/13	3/17
DIT followed by surgery	1	10	SD: 1	PR: 1	CR: 1	PR: 1	CR: 1	1/0	0/1
ICE followed by DIT	1	ICE: 2 DIT: 5	MR: 1	CR: 1	CR: 1	CR: 1	CR: 1	0/1	0/1
MIBG alone	12	MIBG: 1 (n = 10) 2 (n = 2)	CR: 0 PR: 6 MR: 4 SD: 2	CR: 1 PR: 7 MR: 4 SD: 0	CR: 7 PR: 4 SD: 1 NE: 0[a] Unknown: 0[b]	CR: 2 PR: 8 SD: 1 NE: 1[a] Unknown: 0[b]	CR: 4 PR: 3 MD: 3 SD: 0 NE: 2[a] Unknown:0[b]	7/5	5/7
MIBG followed by DIT	2	MIBG: 1 (n = 2) DIT: 5 (n = 1) 3 (n = 1)	SD: 2	CR: 1 PR: 1	CR: 2	CR: 1 PR: 1	CR: 2	0/2	0/2
I/T followed by MIBG	4	I/T: 1-6 MIBG: 2 (n = 1) 1 (n = 3)	CR: 0 PR: 0 MR: 3 SD: 1	CR: 0 PR: 3 MR: 1 SD: 0	CR: 4 PR: 0 SD:0 NE:0[a] Unknown: 0[b]	CR: 0 PR: 3 SD: 1 NE:0[a] Unknown: 0[b]	CR: 2 PR: 1 MD: 1 SD: 0 NE: 0[a] Unknown: 0[b]	2/2	2/2
I + bortezomib followed by MIBG	1	MIBG: 1 (n = 1)	MR: 1	PR: 1	CR: 1	PR: 1	CR: 1	1/0	0/1
I/T followed by MIBG plus I/V	1	IT: 1 MIBG + I/V: (n = 1)	MR: 1	PR: 1	CR: 1	PR: 1	CR: 1	1/0	0/1
Surgery and MIBG	2	MIBG: 1 (n = 2)	CR: 0 PR: 1 MR: 0 SD: 1	CR: 0 PR: 1 MR: 1 SD: 0	CR: 0 PR: 2 SD:0 NE:0[a] Unknown: 0[b]	CR: 0 PR: 1 SD: 1 NE:0[a] Unknown: 0[b]	CR: 0 PR: 2 MD:0 SD:0 NE:0[a] Unknown: 0[b]	2/0	1/1
Cyclo/Topo	3	2 (n = 1) 1 (n = 1) Unknown (n = 1)	CR: 0 PR: 3 MR: 0 SD: 0	CR: 1 PR: 1 MR: 0 SD: 0 Unknown:1[b]	CR: 2 PR: 0 SD: 0 NE: 0[a] Unknown: 1[b]	CR: 2 PR: 0 SD: 0 NE: 0[a] Unknown: 1[b]	CR: 1 PR: 1 MD: 0 SD: 0 NE: 0[a] Unknown: 1[b]	1/2	1/2

TABLE 3. *Continued*

Bridge Therapy	No. of Patients	No. of Bridge Treatment Cycles	End-Induction Overall INRC Response, No.	End-of-Bridge Overall INRC Response, No.	End-of-Bridge Primary Tumor Response, No.	End-of-Bridge Metastatic Bone and Soft Tissue Response, No.	End-of-Bridge Bone Marrow Response, No.	Event: Y/N	Death: Y/N
ICE followed by Cyclo/Topo and surgery	1	ICE: 2 Cyclo/Topo: 2	MR: 1	SD: 1	CR: 1	SD: 1	CR: 1	0/1	0/1
Cixutumumab and temsirolimus (ADVL1221) followed by surgery	1	1	MR: 1	CR: 1	CR: 1	CR: 1	CR: 1	1/0	1/0
I/T followed by surgery	1	1	MR: 1	MR: 1	PR: 1	SD: 1	MR: 1	1/0	1/0
External-beam radiation	1	NA	PR: 1	PR: 1	PR: 1	CR: 1	PR: 1	0/1	0/1

Abbreviations: CR, complete response; Cyclo/Topo, cyclophosphamide and topotecan; DIT, dinutuximab, irinotecan, and temozolomide; ICE, ifosfamide, carboplatin, and etoposide; I, irinotecan; INRC, International Neuroblastoma Response Criteria; I/T, irinotecan and temozolomide; I/V, irinotecan and vincristine; MD, minimal disease; MIBG, meta-iodobenzylguanidine; MR, minor response; NA, not applicable; NE, not evaluable; PR, partial response; SD, stable disease; Y/N, yes/no.
[a]The response was not evaluable. The site was not involved at diagnosis and remained uninvolved.
[b]Unknown response of evaluable disease.

TABLE 4. Cohort 2 Disease Response and Outcome According to the Bridge Regimen

Bridge Regimen	No. of Patients	End-Induction Overall INRC Response, No.	End-of-Bridge Overall INRC Response, No.	2-y EFS/2-y OS, % (95% CI)	3-y EFS/3-y OS, % (95% CI)	5-y EFS/5-y OS, % (95% CI)
Regimen contains DIT without MIBG	22	CR: 0	CR: 8	67.8 (41.7-84.2)	52.7 (26.3-73.6)	NA
		PR: 7	PR: 11	95.2 (70.7-99.3)	87.3 (56.4-96.8)	
		MR: 11	MR: 3			
		SD: 4	SD: 0			
Regimen contains MIBG without DIT	20	CR: 0	CR: 1	75.0 (50.0-88.7)	50.0 (27.1-69.2)	50.0 (27.1-69.2)
		PR: 7	PR: 13	95 (69.5-99.3)	85.0 (60.4-94.9)	63.5 (38.0-80.8)
		MR: 9	MR: 6			
		SD: 4	SD: 0			
Regimen contains both MIBG and DIT	2	SD: 2	CR: 1	100	100	NA
			PR: 1	100	100	
Regimen without MIBG and DIT	7	CR: 0	CR: 2	85.7 (33.4-97.9)	57.1 (17.2-30.5)	57.1 (17.2-30.5)
		PR: 4	PR: 2	100	85.7 (33.4-97.9)	51.4 (11.8-81.3)
		MR: 3	MR: 1			
		SD: 0	SD: 1			
			Unknown:1[a]			

Abbreviations: CR, complete response; DIT, dinutuximab, irinotecan, and temozolomide; EFS, event-free survival; INRC, International Neuroblastoma Response Criteria; MIBG, meta-iodobenzylguanidine; MR, minor response; NA, not applicable; PR, partial response; SD, stable disease.
[b]Unknown response of evaluable disease.

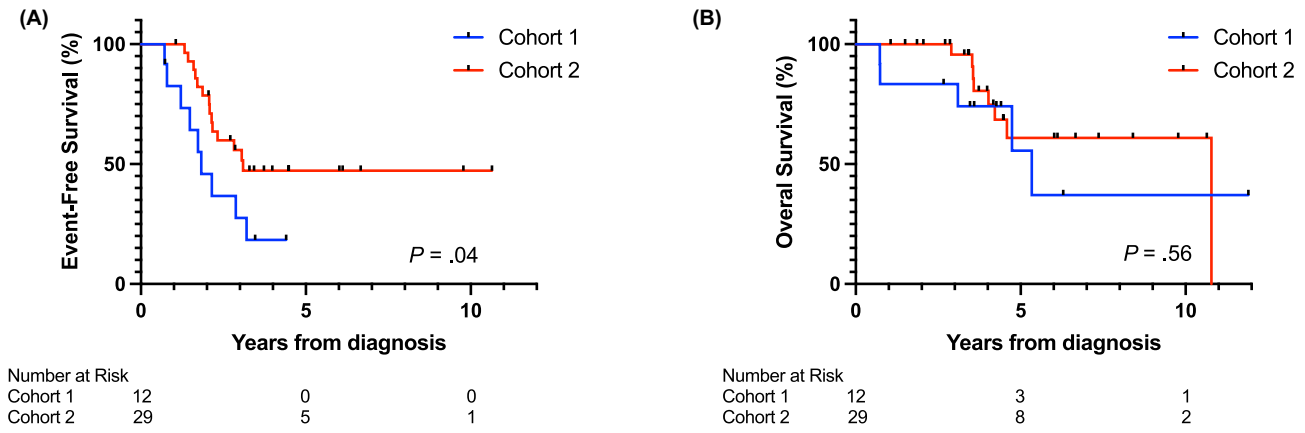


FIGURE 3. Probability of (A) event-free survival and (B) overall survival for cohort 1 and cohort 2 patients with stable disease at metastatic sites at the end of induction.

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CONFLICT OF INTEREST DISCLOSURES

Ami V. Desai reports stock ownership in Pfizer and Viatris; consultancy/advisory board fees from Merck, Ology Medical Education, and Y-mAbs Therapeutics; and travel and accommodation expenses from GlaxoSmithKline. Mark A. Applebaum reports consultancy/advisory board fees from Fennec Pharmaceuticals and Innervate Radiopharmaceuticals. Jennifer H. Foster has served on an advisory board for Y-mAbs Therapeutics and reports consulting fees from Y-mAbs Therapeutics and Alkermes. Navin Pinto reports honoraria from PlatformQ and participation on an advisory board for Y-mAbs Therapeutics. Michele Nassin reports that since the completion of her involvement in this study, she has joined Novartis Pharmaceuticals. Rochelle Bagatell is an uncompensated member of a Y-mAbs Therapeutics advisory board. Susan L. Cohn reports stock ownership in Pfizer, Merck, and Lilly; has received honoraria from Ology Medical Education; and has served on an advisory board for Y-mAbs Therapeutics. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Ami V. Desai: Conceptualization, data curation, writing–original draft, writing–review and editing, and supervision. **Mark A. Applebaum:** Formal analysis and writing–review and editing. **Theodore G. Karrison:** Formal analysis and writing–review and editing. **Akosua Oppong:** Data curation and writing–review and editing. **Cindy Yuan:** Data curation and writing–review and editing. **Katherine R. Berg:** Data curation and writing–review and editing. **Kyle MacQuarrie:** Data curation and writing–review and editing. **Elizabeth Sokol:** Data curation and writing–review and editing. **Anurekha G. Hall:** Data curation and writing–review and editing. **Navin Pinto:** Data curation and writing–review and editing. **Ian Wolfe:** Data curation and writing–review and editing. **Rajen Mody:** Data curation and writing–review and editing. **Suzanne Shusterman:** Data curation and writing–review and editing. **Valeria Smith:** Data curation and writing–review and editing. **Jennifer H. Foster:** Data curation and writing–review and editing. **Michele Nassin:** Data curation and writing–review and editing. **James LaBelle:** Data curation and writing–review and editing. **Rochelle Bagatell:** Data curation and writing–review and editing. **Susan L. Cohn:** Conceptualization, data curation, writing–original draft, writing–review and editing, and supervision.

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