

Effects of preoperative chemotherapy on neuroblastoma with *MYCN* amplification: a surgeon's perspective

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ABSTRACT

Background Preoperative chemotherapy plays an important role in the surgical management of unresectable neuroblastoma. Its response to chemotherapy has been variable due to the tumor's heterogeneity. We aimed to evaluate the effects of preoperative chemotherapy on *MYCN*-amplified (MYCNA) neuroblastoma that would impact on surgical resection.

Methods Patients with MYCNA neuroblastoma who received preoperative chemotherapy followed by surgical resection performed at our center were included. The tools of response evaluated included tumor volume reduction (TVR), reduction in image-defined risk factors (IDRFs), percentage tumor necrosis (Nec), and surgical complications.

Results Among 62 patients evaluated, mean age was 3.0 (range, 0.9–11.8) years, and primary tumors were distributed in the abdomen (n=59), pelvis (n=2), and thorax (n=1). The patients were in stages L2 (n=14) and M (n=48). Surgery was performed after median of 4 (range, 2–10) cycles of chemotherapy. On completion of preoperative chemotherapy, 41 (66.1%) patients had TVR >65%, 24 (42.9%) responded with reduced IDRFs, 47 (75.8%) tumors had Nec >50%, and 27 patients suffered 31 surgical complications. Majority (83.9%) continued to have IDRFs at surgery. IDRFs commonly encountered were encasement of renal pedicles (n=50), superior mesenteric artery (n=46), celiac axis (n=45), and aorta/vena cava (n=44), and most remained refractory to resolution. Patients with TVR >65% were associated with Nec >50% (87.5% vs 54.5%, p=0.004) and reduced IDRFs (46.3% vs 19%, p=0.035), but not with the incidence of surgical complications.

Conclusions Majority of MYCNA neuroblastomas were highly chemosensitive as they experienced high TVR, reduced IDRFs, and high Nec, and hence created favorable conditions for surgical resection. Poor responders and persistent IDRFs that were commonly refractory to preoperative chemotherapy remained a surgical challenge.

INTRODUCTION

MYCN amplification (MYCNA) has been present in 20% of patients with neuroblastoma and is correlated with an undifferentiated, aggressive phenotype and poor prognosis.^{1,2} Therefore, these patients have been stratified to the high-risk group, receiving intensive treatment.

Key messages

What is already known about this subject?

- ▶ Neuroblastoma with *MYCN* amplification is often unresectable at diagnosis.
- ▶ Its response to chemotherapy could be variable.
- ▶ Surgical resection is essential in neuroblastoma treatment.

What are the new findings?

- ▶ Neuroblastoma with *MYCN* amplification shows remarkable response to chemotherapy.
- ▶ Preoperative chemotherapy results in significant tumor volume reduction.
- ▶ Preoperative chemotherapy results in significant tumor necrosis.
- ▶ Preoperative chemotherapy results in reduction of image-defined risk factors.

How might it impact on clinical practice in the foreseeable future?

- ▶ This paper illustrates the remarkable effects of preoperative chemotherapy and its impact on surgery of neuroblastoma. It potentially provides early preoperative guidance at diagnosis.

Preoperative chemotherapy has continued to play an important role in the management of unresectable neuroblastoma.³ Besides being a systemic treatment that targets on metastases, its chemotherapeutic effects on the primary tumor sites can be significant. Indeed, primary tumors' responsiveness to preoperative chemotherapy has been shown to be predictive of treatment outcome⁴ and more specifically in MYCNA tumors.⁵

Unlike non-MYCNA tumors, we noticed that MYCNA tumors often demonstrated larger tumor volume reduction, tumor necrosis, and reduction in image-defined risk factors (IDRFs) after receiving neoadjuvant chemotherapy.⁶ These responses potentially created favorable conditions to achieve the surgical goal of ≥90% surgical resection with less surgical complications.⁷ The aim of this study was to determine the effects of preoperative



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chemotherapy that might have a direct impact on surgery for MYCNA neuroblastoma.

METHODS

A retrospective review of our center's Neuroblastoma Database from June 2007 to May 2019 was conducted. Among a total of 302 patients, 62 (20.5%) with pathological diagnosis of MYCNA neuroblastoma who had received preoperative chemotherapy of any protocols and had undergone surgical resection at our center were included in the study. Patients' clinical charts, CT and MRI scans, and histopathological reports were reviewed and analyzed. Patients were staged according to the INRGSS (International Neuroblastoma Risk Group Staging System).⁶

Patients' imaging scans were evaluated at two time-points, namely before and after preoperative chemotherapy, to compare the primary tumor volumes and IDRFs. The patients' feasibility to undergo surgical resection was based on the primary surgeon's assessment on completion of preoperative chemotherapy. None of the patients had documented tumor progression or significant bone marrow metastases at completion of preoperative chemotherapy. All patients studied underwent their best surgical resection achieving $\geq 90\%$ resection.

Response measures that were known to affect the safe conduct of surgery were studied. These included tumor volume reduction (TVR), reduction in IDRFs, percentage tumor necrosis (Nec), and surgical complications. Tumor volume was measured from imaging studies using the formula ($\pi/6 \times \text{antero-posterior} \times \text{width} \times \text{craniocaudal measurements}$). TVR, if present, was then expressed as a percentage and categorized into $>65\%$, $50\%–65\%$, and $<50\%$. The number of IDRFs was compared at similar time-points and patients were categorized as "reduced IDRFs" if there was resolution of one or more IDRFs. Nec score was reported routinely as per our institution's histopathology protocol. They were categorized as $>90\%$, $50\%–90\%$, and $<50\%$ in this study. For consistency in this manuscript, these response measures will be abbreviated without the "%" symbol (such as "TVR >65 " for TVR $>65\%$). Postoperative complications were recorded as documented in the database. Statistical analysis was performed using the χ^2 and Fisher's exact tests. Statistical significance was attained when p value was <0.05 . Overall survival was estimated using Kaplan-Meier survival analysis.

Our surgical team operated at a tertiary referral center for pediatric surgical oncology and we received patients from various institutions with diverse treatment regimens. Detailed information of treatment protocols was usually limited and could not be systematically categorized for analysis.

RESULTS

Sixty-two patients were identified with mean age of 3 (range, 0.9–11.8) years. The male:female ratio was 34:28.

The primary tumor sites were in the abdomen ($n=59$), pelvis ($n=2$), and thorax ($n=1$). The patients were in stages L2 ($n=14$) and M ($n=48$). Chromosomal aberrations identified included deletions of chromosome 1p ($n=19$), chromosome 11q ($n=6$), and gain of chromosome 17q ($n=3$). Surgery was performed after a median of 4 (range, 2–10) cycles of chemotherapy, categorized as 2 to 5 ($n=53$) and >5 ($n=9$) cycles.

Response measures

Forty-one (66.1%) patients attained TVR >65 after preoperative chemotherapy, while 12 (19.4%) achieved TVR $50–65$. Only nine (14.5%) patients responded poorly with TVR <50 .

Fifty-six (90.3%) patients had IDRFs at initial diagnosis. Six patients who had no IDRFs but had metastases were classified as stage M. After chemotherapy, 24 (42.9%) patients showed reduced IDRFs of which four had complete resolution of IDRFs. The four most common IDRFs present at diagnosis included encasement of renal pedicles, including tumor that was only in contact with renal vessels (89.3%), encasement of superior mesenteric artery (SMA) (82.1%), celiac axis (80.4%), and aorta/vena cava (78.6%). The IDRFs that were most refractory to chemotherapy were encasement of renal pedicles (6% resolution), aorta/vena cava (9.1% resolution), celiac axis (17.8% resolution), and SMA (17.4% resolution).

At histopathological examination, 47 (75.8%) tumors reported Nec >50 among which 28 had Nec >90 . There were 15 (24.2%) found to have Nec <50 .

A total of 27 patients suffered 31 surgical complications. Two patients underwent concurrent nephrectomy as the invasion of the kidney was deemed too extensive to spare the kidney, three patients underwent subsequent nephrectomy because of local relapse in the renal parenchyma, and three kidneys underwent postoperative renal atrophy detected at imaging studies performed 3 to 6 months after surgery. Twelve patients developed postoperative chylous fistulae of which three required laparotomy and surgical repair. Six patients developed intestinal obstruction of which two required surgical adhesiolysis. Two developed biliary stenosis requiring stenting for 4 weeks, and three developed adrenal insufficiency that required replacement therapy. Neither TVR nor Nec was significantly associated with the occurrence of surgical complications.

Association among response measures

More patients with TVR >65 were associated with Nec >50 than patients with TVR <65 (87.5% vs 54.5%, $p=0.004$). The difference remained statistically significant when Nec >90 was evaluated (57.5% vs 22.7%, $p=0.009$).

Patients who achieved TVR >65 were more likely to be associated with reduced IDRFs (46.3% vs 19%, $p=0.035$).

Patients with reduced IDRFs were not more likely to be associated with Nec >50 (87% vs 69.2%, $p=0.45$); however, reduced IDRFs, if present, was associated with Nec >90 (65.2% vs 33.3%, $p=0.02$).

Analysis of factors that may influence response measures

Three factors were evaluated to study their effects on the response measures. These included the presence of pre-treatment *MYCN* testing, the presence of metastases at diagnosis, and age at diagnosis (table 1).

Twenty-seven (43.5%) patients did not receive pre-treatment *MYCN* testing. They were confirmed with *MYCN*A when tumor tissue samples were submitted for Fluorescence In Situ Hybridization (FISH) analysis at the time of surgery. As a result, 10 patients were pre-treated according to intermediate-risk instead of high-risk protocol. There were seven with non-metastatic disease, and three with metastatic disease were <1.5 years of age. They showed excellent response as 80% achieved TVR>65 while all developed Nec>50. The lack of pre-treatment *MYCN* testing did not have an adverse impact on any of the response measures.

The presence of metastases did not affect the tumors' response to chemotherapy with regards to TVR, necrosis, and reduced IDRFs. However, more non-metastatic patients were found to have developed surgical complications than patients with metastases (78.6% vs 33.3%, $p=0.005$). This, in turn, did not correlate with less intensive treatment received by those who lacked pre-treatment *MYCN* testing (71.5% vs 85.7%, $p=1$).

Younger patients, aged <1.5 years, were more likely to achieve Nec>50 than older patients (94.1% vs 68.9%, $p=0.049$). Otherwise, age at diagnosis did not affect the tumors' response to chemotherapy with regards to TVR, reduced IDRFs, and surgical complications.

The patients were followed up for mean period of 2.6 (range, 0.3–9.8) years. Considering that 21 (33.9%) were lost to follow-up, 5 died of other conditions, 12 had no evidence of disease, 1 was alive with disease, and 23 died of disease; 3-year overall survival was 48.8%.

DISCUSSION

*MYCN*A neuroblastoma is often unresectable at initial diagnosis because of its size, location or IDRFs, and vascularity.^{8,9} The efficacy of current neoadjuvant therapy can render infiltrative tumors more readily resectable with less risks.¹⁰ A tumor's resectability takes into consideration all of the aforementioned factors and a surgeon's judgment that the surgical goal can be met with minimal morbidity. From the surgeon's perspective, the ability to predict a tumor's response to chemotherapy allows the opportunity for adequate surgical planning.

We selected four response measures that were believed to be related to the safe conduct of surgery. The reduction in tumor volume during induction chemotherapy had been reported to be predictive of outcome in high-risk neuroblastoma.^{4,5} Such a response would have significant surgical implications as it would decrease tumor vascularity and hence improve tumor resectability.¹¹ IDRFs were surgical risk factors introduced in the INRGSS.⁶ Although these factors were not contraindications to surgery, they had been predictive of outcome,

Table 1 Analysis of three factors' influence on response measures

	TVR>65 n (%)	TVR<65 n (%)	P value	Nec>50 n (%)	Nec<50 n (%)	P value	Reduced IDRF n (%)	No reduced IDRF n (%)	P value	Complication Yes n (%)	Complication No n (%)	P value
Pretreatment MYCN testing												
Yes	22 (62.9)	13 (37.1)	0.79	25 (71.4)	10 (28.6)	0.39	16 (45.7)	19 (54.3)	0.12	14 (40)	21 (60)	0.61
No	18 (66.7)	9 (33.3)		22 (81.5)	5 (18.5)		7 (25.9)	20 (74.1)		13 (48.1)	14 (51.9)	
Metastases												
Yes	30 (62.5)	18 (37.5)	0.35	34 (70.8)	14 (29.2)	0.16	16 (33.3)	32 (66.7)	0.35	16 (33.3)	32 (66.7)	0.005*
No	11 (78.6)	3 (21.4)		13 (92.9)	1 (7.1)		7 (50)	7 (50)		11 (78.6)	3 (21.4)	
Age at diagnosis (y)												
<1.5	14 (82.4)	3 (17.6)	0.14	16 (94.1)	1 (5.9)	0.049*	8 (47.1)	9 (52.9)	0.4	10 (58.8)	7 (41.2)	0.16
>1.5	27 (60)	18 (40)		31 (68.9)	14 (31.1)		16 (34.8)	30 (65.2)		17 (37.8)	28 (62.2)	

*Denotes statistical significance if $p<0.05$.
IDRF, image-defined risk factor; TVR, tumor volume reduction.

surgical complications, and the completeness of resection.^{12–14} The resolution of these factors was used here as a response measure for preoperative chemotherapy. The amount of tumor necrosis represented the tumor's histological response to preoperative chemotherapy. Tumor necrosis would be considered a predisposition for less bleeding at tumor dissection. The incidence of surgical complications was chosen as a response measure as these were typically related to the difficulty of the surgery.

When compared with Bagatell *et al*'s study,⁵ we found a similar proportion (86%) of MYCNA patients achieved TVR>50. However, we saw significantly fewer patients achieved TVR>65 than published (66% vs 87%, $p=0.003$). The reason behind this result remained unclear, but it could be related to the lack of compliance to standardized protocols across our referring centers. It was also noteworthy to learn from the same reference study that even though volume-based response assessment was not associated with the extent of tumor resection, it was predictive of survival. In our study, significantly more patients with TVR>65 experienced reduced IDRFs and Nec>50 as well, hence more favorable conditions for surgery.

In the International Neuroblastoma Risk Group (INRG) concept, patients with at least one IDRF have potential surgical risks, and the implication of proportionate resolution of IDRFs has not yet been discussed. In our experience, even the resolution of one or few, but not all, IDRFs would have reduced surgical risks and led to safer surgeries. Only few in our cohort had complete disappearance of IDRFs while more showed numerical reduction after preoperative chemotherapy. Despite larger TVR (>65), only 46% had reduced IDRFs after chemotherapy. This proportion was significantly higher than those with smaller TVR. At the time of surgery, 83.9% continued to have one or more IDRFs. The four most common IDRFs were also most refractory to resolution, namely, renal pedicles, SMA, celiac axis, and aorta/inferior vena cava. We believed these sites represented the tumors' origin in peri-arterial sympathetic nervous system.

When compared with non-MYCNA tumors, MYCNA neuroblastoma had been known to be associated with significantly more tumor necrosis after chemotherapy.¹⁵ Our study showed similar findings where 76% of tumors achieved Nec>50, of which 60% had Nec>90.

Previous publications have reported that tumor response was most prominent in the first few cycles of chemotherapy.^{11,16} Those who required more may have acquired chemoresistance. As our patients received diverse treatment protocols with many lacking in details of treatment, we were not able to make reasonable inference. Nevertheless, we believed there was a misconception that more chemotherapy could further reduce IDRFs that were present.

MYCN testing was not consistently available in some of the referring centers in the early half of this decade. Awareness and availability of MYCN testing has

improved with time. In its absence, 10 patients received less intensive treatment when they were stratified to intermediate-risk group protocols. Nevertheless, these MYCNA tumors showed remarkable chemosensitivity, with 80% achieving TVR>65 and 100% Nec>50.

The presence of metastatic disease was not associated with TVR, reduced IDRFs, and Nec. However, it was noteworthy that non-metastatic patients were significantly more prone to develop surgical complications, and the underlying reasons were unclear. Though all MYCNA patients were stratified as high-risk group regardless of age, patients <1.5 years were more chemoresponsive, achieving Nec>50.

In conclusion, the majority of our MYCNA neuroblastoma were highly chemo-sensitive. They were good responders to preoperative chemotherapy as they experienced high TVR, reduced IDRFs, and high Nec, and hence favorable conditions were created for surgical resection. Poor responders and persistent IDRFs were commonly refractory to chemotherapy, and they remained a surgical challenge.

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Data availability statement Data are available on reasonable request. The database is stored as a deidentified database.

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