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The optimal timing of surgical resection in high-risk neuroblastoma

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ABSTRACT

Background: While most high-risk neuroblastoma (HRNB) patients are enrolled in cooperative group or institutional protocols, variability exists within these protocols as to when surgical resection of the primary tumor should be performed after neoadjuvant induction chemotherapy. We sought to determine if the number of chemotherapy cycles prior to surgery affects surgical or survival outcomes in HRNB patients.
Methods: We performed a retrospective review of all HRNB patients <18 years of age from 2000 to 2010, at Texas Children's Hospital. Patients were stratified based on the number of neoadjuvant induction chemotherapy cycles prior to surgical resection. Pre and post- chemotherapy tumor size, MYCN status, iodine-131-metaiodobenzylguanidine (MIBG) score at diagnosis, extent of surgical resection, estimated surgical blood loss, post-operative outcomes, and event free (EFS) and overall survival (OS) were evaluated. Data were analyzed using Wilcoxon rank-sum test, Kruskal–Wallis test, Fisher's exact test, Kaplan–Meier analyses, and Cox regression analyses. *P*-value <0.05 was considered significant.
Results: Data from 50 patients with HRNB were analyzed. Patients were stratified by the number of cycles of chemotherapy received prior to surgery. Six patients received 2 cycles of chemotherapy (12%), 20 patients received 3 cycles (40%), 13 patients received 4 cycles (26%), and 11 patients received 5 cycles (22%) prior to surgical resection of the primary tumor. The 5-year OS was 33%, 45%, 83% and 36% in patients who received 2, 3, 4 and 5 cycles of chemotherapy prior to surgery, respectively ($p = 0.07$). Multivariate analysis revealed that patients who received 4 cycles of chemotherapy had a significantly lower mortality (HR: 0.11, 95% CI: 0.01–0.87, $p = 0.04$) compared to those with 2 cycles of chemotherapy. Among the different cohorts, there were no differences with respect to MYCN status, MIBG score at diagnosis, incidence of bone marrow metastasis, extent of surgical resection, estimated blood loss, incidence of post-operative complications, or length of stay.
Conclusion: HRNB patients who receive 4 cycles of chemotherapy prior to surgical resection have a superior OS than patients who receive 2. Based on the superior survival of patients who received 4 cycles of chemotherapy prior to surgery, further studies are warranted to elucidate these differences.

Neuroblastoma is the most common extracranial solid tumor in children, arising from neural crest cells that differentiate to the sympathetic ganglia and adrenal medulla [1]. It accounts for 7% of all malignancies in children and 10–15% of cancer-related deaths in childhood [1,2]. NB is a heterogeneous disease, and its clinical course can range from spontaneous regression to very aggressive, metastatic and progressive disease. Patients with high-risk neuroblastoma (HRNB) are at an increased risk for rapid progression and relapse [2]. Despite multimodal therapy, 50% of patients with newly diagnosed HRNB, and less than 10% of patients with relapsed HRNB, will survive [1].

Current therapy for HRNB consists of some combination of intensive multi-agent induction chemotherapy, surgery, radiation, myeloablative consolidation therapy with stem cell rescue and transplantation, 13-*cis* retinoic acid and immunotherapy [1–4]. The role of surgical resection of the primary tumor in HRNB is controversial with conflicting studies in the literature regarding the benefit of aggressive surgery in this group [5,6]. Currently, the Children's Oncology Group (COG) recommends aggressive surgical resection of the primary tumor with the goal of gross total resection [2,7]. This current recommendation is supported by the

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recent results of two studies from the COG and the International Society of Pediatric Oncology Europe Neuroblastoma (SIPOEN), which demonstrated benefit and improved survival with gross total resection [7,8]. However, unlike the treatment of other pediatric solid tumors, such as rhabdomyosarcoma and Ewing's sarcoma, which clearly define when surgery and radiation should occur, the optimal timing for surgical resection in HRNB has not been well defined, and thus the decision is left to the discretion of individual oncologists and surgeons. At different institutions, some patients may undergo surgery after the last cycle of induction chemotherapy, while others advocate for an earlier surgical intervention, based on when the tumor appears resectable on imaging [9]. The purpose of this study was to determine if the number of chemotherapy cycles prior to surgical resection affects surgical or survival outcomes in HRNB patients. Our hypothesis is that patients treated with less neoadjuvant chemotherapy would have larger pre-resection tumors, more difficult resections and thus higher post-operative complication rates and worse overall survival.

1. Methods

1.1. Patients and study design

This is a retrospective study of all patients ≤18 years of age diagnosed with HRNB at our institution from 2000 to 2010. Patients were included if they were ≤18 years of age, had a diagnosis of HRNB based on the Children's Oncology Group (COG) risk stratification and underwent surgical resection of their primary tumor.

Our study focused on HRNB patients who presented with unresectable primary tumors at diagnosis. Patients (n = 10) with resectable tumors who did not receive neoadjuvant chemotherapy prior to surgery were excluded. The upfront resection patients presented with smaller tumors (mean 5.0 cm greatest diameter) at the time of diagnosis and were resected prior to receiving any chemotherapy. In addition, patients with no primary tumor (n = 2) and patients who underwent surgical resection of the primary tumor at another facility (n = 9) were excluded from this analysis. Moreover, a patient with a simultaneous diagnosis of Ewing's sarcoma and HRNB, a patient who had no chemotherapy treatment because of pre-existing cardiomyopathy, and a patient with incomplete medical records were excluded.

1.2. Data collection

All clinical data were obtained from electronic and paper medical records. Collected variables included patient demographics, age at the time of diagnosis, stage based on the International Neuroblastoma Staging System (INSS) [10], International Neuroblastoma Risk Group (INRG) stage [11,12], MYCN status, Shimada histology, bone marrow status at diagnosis, MIBG score [13] at the time of diagnosis, induction chemotherapy protocol, number of chemotherapy cycles prior to surgical resection of primary tumor, tumor volume reduction, extent of resection, estimated blood loss (EBL), intraoperative and post-operative complications, length of hospital stay, and status at the end of follow-up. Minor post-operative complications included post-operative fever, Horner's syndrome, hypovolemia, and ileus. Major post-operative complications included chylous ascites or chylothorax, post-operative hemorrhage (defined as loss of >30% blood volume), bacteremia, adrenal insufficiency and death.

1.3. Treatment protocols and surgery

All patients in this study were treated with a multidisciplinary approach that consisted of high-dose chemotherapy, surgery, radiotherapy, autologous stem cell transplantation, and 13-*cis* retinoic acid. Two patients from this cohort were treated on the COG ANBL0032 study evaluating chimeric 14.18 immunotherapy with 13-*cis* retinoic acid. The time period of this study spanned 2 different induction chemotherapy regimens used at our institution: PEPI (an institutional review board approved [IRB] Phase II institutional research protocol) and COG ANBL00P1. The treatment protocol offered to each patient was dependent on which protocol was open or the institutional standard at the time of patient presentation. The PEPI induction chemotherapy protocol used a combination of cisplatin, etoposide, cyclophosphamide, and doxorubicin. ANBL00P1 consisted of vincristine, ifosfamide, and carboplatin, in addition to those used in the PEPI protocol. Patients were placed on an individualized protocol with dose reduction of either PEPI or ANBL00P1 chemotherapy agents if they demonstrated renal or organ dysfunction and/or drug toxicity. All induction protocols in this study were a total of 5 cycles. Surgical resection of the primary tumor was performed by one of two experienced pediatric surgeons at our institution. The goal of surgery for all cases was complete resection, defined as removal of >90% of gross total tumor volume. The extent of tumor resection was determined by the surgeon's operative report. The decision to operate was made by multi-disciplinary consensus based on imaging and efficacy of chemotherapy, such that patients who did not appear to have significant tumor reduction with additional chemotherapy cycles underwent surgical resection. Surgical resection after cycle 2–5 was allowed for patients enrolled on PEPI, after cycle 4 or 5 if patients were enrolled on ANLB00P1 and at the discretion of the multidisciplinary team for all patients not enrolled on a clinical trial.

1.4. Metaiodobenzylguanidine (MIBG) scoring system

The scoring method for MIBG scans performed at the time of diagnosis was based on criteria outlined by Messina et al. [13]. The patient's skeleton was divided into 9 segments to assess bone lesions and a 10th segment to assess soft tissue involvement [13]. Extension and intensity scores were assigned to each segment to quantify the extent and degree of MIBG uptake. Extension score was graded as follows: 0, no sites per segment; 1, one site per segment; 2, more than one site per segment; and 3, diffuse involvement (>50% of the segment). Intensity score was graded as follows: 0, no uptake; 1, doubtful uptake; 2, obvious uptake; and 3, strong uptake. The maximum extension and intensity scores are 30 and 30, respectively. All MIBG scans were reviewed and scored by a pediatric radiologist (N.M.) blinded to the patient's outcome.

1.5. Tumor volumes

To determine the extent of tumor reduction with chemotherapy, computed tomography (CT) scans at the time of diagnosis and prior to surgery were reviewed by a pediatric radiologist (K.L.) blinded to the number of chemotherapy cycles of each patient at the time of the scan. Tumor volume (cm^3) was calculated using the following formula: maximal orthogonal tumor length × width × height × 0.52 (π/6). Tumor volume reduction was calculated as the difference between tumor volume at the time of diagnosis and prior to surgery.

1.6. Statistical analyses

Patients were stratified by the number of chemotherapy cycles received prior to surgical resection. As the HRNB patients represented unresectable tumors at the time of diagnosis, and since none of the patients underwent one cycle of chemotherapy prior to surgical resection, the 2 cycle group serves as our minimum chemotherapy control group, and cohorts of patients who received additional cycles of chemotherapy were compared to this group. Data were summarized and compared between groups using non-parametric Wilcoxon rank-sum test or Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. Kaplan–Meier analyses were used to estimate overall survival (OS) and event free survival (EFS). Cox regression analyses were performed to determine the association between the number