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Is high risk neuroblastoma induction chemotherapy possible without G-CSF? A pilot study of safety and treatment delays in the absence of primary prophylactic hematopoietic growth factors

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Abstract

Background/Objectives—Standard supportive care during induction therapy for high-risk neuroblastoma (HR-NBL) includes primary prophylacticgranulocyte colony stimulating factor (G-CSF) aimed at limitingduration of neutropenia, reducing infection risk, and minimizingtreatment delays. Preclinical models suggest that G-CSF promotes maintenance of neuroblastoma cancer stem cells and may reduce the efficacy of chemotherapy. This study's objective was to determine the safety and feasibility of administering induction chemotherapy without routine use of prophylactic G-CSF.

Design/Methods—Children with newly diagnosed HR-NBLreceived six-cycle induction chemotherapy regimen without prophylactic G-CSF in 4 cycles.G-CSF was administered for stem cell mobilization after cycle 3 andGranulocyte-monocyte colony stimulating factorafter cycle 5 prior to surgical resection of primary disease. The primary outcome measure was theincidence of grade 3 or higher infection. We hypothesized that the per patient infection rate would be

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Conflict of Interest
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Data Availability Statement: the data that support the findings of this study are openly available at https://www.clinicaltrials.gov/ct2/show/NCT02786719

comparable to our institutional baseline rate of 58% in patients with HR-NBLreceiving induction chemotherapy with prophylactic growth factor support. The trial used an Ahern single stage design.

Results—Twelve patients with HR-NBL received 58 cycles of chemotherapy on study. Three patients completed the entire 6 cycle regimen with no infections. Nine patients experienced grade 3 infections (bacteremia 4, urinary tract infection 2, skin/soft tissue infection 3). No patients experienced grade 4 infections or required intensive care treatment for infection.

Conclusion—A greater than expected number of serious bacterial infections were observed during administration of induction chemotherapy for HRNB without primary prophylactic G-CSF. These results support continued prophylactic administration growth factor during induction chemotherapy.

Keywords

Neuroblastoma; high-risk neuroblastoma; induction chemotherapy; G-CSF; GM-CSF; cancer stem cell

Introduction

High-risk neuroblastoma (HR-NBL)is an aggressive malignancy of childhoodrequiring intensive multimodal treatment typically divided into three phases:induction, consolidation, and maintenance[1]. Induction consists of 5-6 cycles of cytotoxic chemotherapy and surgical resection. In consolidation, patients usually receive 1 or 2 cycles of high dose chemotherapy followed by autologous hematopoietic stem cell rescue and local control with radiation. The final phase, maintenance, combinesimmunotherapy and biologic differentiation agents. Despite this intensive regimen and recent improvements in survival, the 5 year overall survival for these children remains at approximately 50%.[2–5]

Treatment-related myelosuppression with concomitant risk for severe infections is a frequent toxicity throughout this regimen. Recombinant human granulocyte colony stimulating factor (G-CSF)was first tested as a component of neuroblastoma treatment nearly 20 years ago. The first randomized, controlled trial of G-CSF use in children with metastatic neuroblastoma was published in 1998.[6] In this study, the authors noted a reduction in overall neutropenia and antibiotic use, yet no reduction in febrile neutropenia or hospitalization or death associated from neutropenic infections. Additional studies in neuroblastoma have demonstrated modest reductions in duration of neutropenia, incidence of febrile neutropenia and no difference in rate of serious bacterial infections or chemotherapy response rate with or without G-CSF primary prophylaxis.[6–8] Since that time, G-CSF has been included as a standard supportive care measure for children with HR-NB undergoing induction chemotherapy.

Single cell sequencing and epigenetic profiling has clearly illustrated that aggressive malignancies are highly heterogeneous, and that complex signaling networks among tumor/tumor and tumor/host subpopulations confer resistance to treatment.[9–11] Tumor initiating subpopulations (cancer stem cells, CSCs) that self-renew, and asymmetrically divide, and recapitulate entire tumors from small numbers of cells are thought to be a driver of drug

resistance leading torelapse after initial responsiveness to chemotherapy.[12, 13] Recent studies have identified a subpopulation of CSCs in neuroblastomadefined by surface expression of the G-CSF receptor CD114 (encoded by *CSF3R*).[14–16] Preclinical *in vivo* modelsdemonstrate that exogenous administration of G-CSF leads to STAT3 activation in CD114 positive neuroblastoma CSC subpopulations.Transcriptional activation of STAT3, a signaling mechanism critical in neural crest differentiation, promotesthe expansion and activation of genes involved in stemness, dedifferentiation and the ectoderm-to-mesoderm transition and targets oncogenic genes involved in metastasis and angiogenesis.[17, 18] Treatment of *in viv*o orthotopic models of neuroblastoma with G-CSF following chemotherapy lead to increased CD114+ cells in residual tumors and increased bone marrow metastasis, while blocking G-CSF signaling inhibited tumor proliferation and metastasis.[14] Tumor biopsies from patients who had undergone treatment with chemotherapy followed by G-CSF demonstrated enrichment of CD114 positive cells.[15]

The results of these studies and the common use of G-CSF in neuroblastoma protocols prompted us to re-evaluate the need for including G-CSF in HR-NB induction chemotherapy. We report here the results from our clinical pilot study where the primary objective was to determine whether induction chemotherapy could be safely delivered without the routine use of prophylactic G-CSF in patients with HR-NBL.

Methods

Participants and Design

Patients with newly diagnosed HR-NBLwere enrolled in this prospective single center clinical trial between May 2016 and January 2018. Written informed consent was obtained from the patient or guardian prior to enrollment. Assent was obtained as appropriate. The study, NCT02786719, was approved by the Baylor College of Medicine Institutional Review Board.

Inclusion criteria included: 1) Age≥12 months and <18 years at diagnosis, 2) newly diagnosed neuroblastoma or ganglioneuroblastoma, 3) diagnosis of high-risk disease as defined by the Children's Oncology Group criteria [5, 19] 4) no prior systemic chemotherapy aside from localized radiation therapy or 1 cycle of intermediate risk regimen without G-CSF, 5)adequate organ function. Any patient who had previously received G-CSF was excluded.

Treatment Plan

This study encompassed the induction phase of chemotherapy only. The chemotherapy treatment plan followed national best practice at the time of the study opening (Figure 1).[5] G-CSF was administered at 10 mg/m^2/dose to facilitate stem cell mobilization for collection after cycle 3. In preparation for surgical resection of primary disease after cycle 5, granulocyte macrophage colony stimulating factor (GM-CSF) 250 mcg/m^2/dosewas administered until ANC ≥750/μLto allow for surgical resection in a timely and predictable fashion. GM-CSF has previously been shown to have similar efficacy to G-CSF in children.[20]

Cycles of chemotherapy were administered every 21 days, if apost-nadir absolute neutrophil count (ANC) was ≥750/μL and platelet count was ≥75,000/μL.If the ANC parameter was not met by 29 days following the start of the previous cycle, GM-CSF was administered at 250 mg/m^2 daily until ANC met start parameters. GM-CSF was also administered prophylactically for all remaining cycles if a patient developed a grade 3 or higher bacterial or fungal infection per CTCAE v4.0.

Outcomes

This study aimed to assess the safety of providing induction chemotherapy for HR-NBL without primary prophylactic G-CSF. The primary outcomewas the per patient incidence of grade 3 or higher bacterial or fungal infection per CTCAE v4.0.Secondary outcome measures were the incidence and duration of delays in chemotherapy administration due to neutropenia, the incidence of febrile neutropenia, and the response rate to induction chemotherapy as defined by the International Neuroblastoma Response Criteria[21]. Febrile neutropenia was defined as a single temperature of ≥101°F or temperature >100.4° F on two occasions 1 hour apart in the setting of ANC<500/μL. Febrile episodes during a cycle when a grade 3 or higher bacterial or fungal infection was identified werecounted as infection rather than febrile neutropenia.

Statistical Methods

Originally, an 8+13 Simon optimal two-stage design was proposed to test for non-inferiority. However, the study design was revised to use an A'hern single stage design in January 2018 to adjust for patient enrollment.[22] Sample size was calculated based on our institutional rate of 58% of patients with high risk neuroblastoma having one or more infections during induction chemotherapy when G-CSF or pegylated G-CSF was administered starting 24-72 hours following completion of each chemotherapy cycle.[23] The null hypothesis was that the proportion of patients who do not develop an infection was less than or equal to 22%. The alternative hypothesis was that the proportion of patients who do not develop an infection was at least 42%. The study would reject the null hypothesis in favor of the alternative if at least five of 13 subjects completed all six cycles of therapy without an infection, demonstrating that the infection rate was not higher with omission of primary prophylactic G-CSF.If thetrue proportion is 22%, then the probability of incorrectly rejecting the null hypothesis is 15% (type 1 error). If the true proportion is 42%, then the probability of failing to reject the null hypothesis is 30% (type II error).Secondary endpoints were analyzed using descriptive statistics.

Results

Characteristics of study participants

Thirteen patients were enrolled on the study betweenJune 2016 andDecember 2018; twelve were evaluable for the primary outcome.The ineligible patient was withdrawn from study due to a surgical complication occurring prior to initiation of chemotherapy. Demographic and disease characteristics of the 12 evaluable patients are presented in Table 1. The median age was 2.9 years (range 1.1 to 6.7 years). Eight patients completed all 6 cycles of induction chemotherapy on study. One patient was removed from protocol therapy after cycle 1 for a

toxicity requiring change in chemotherapy administration, twowere removeddue to withdrawal of parental consent, and onepatient transferred to another institution midway through protocol therapyandconsequently was withdrawn. All patients who were withdrawn from the study experienced grade 3 infection prior to withdrawal and were therefore evaluable for the primary endpoint. A total of 58 cycles of chemotherapy were administered on study. Patients received prophylactic growth factor with G-CSF or GM-CSF in 26 (44.8%) of these cycles.

Infections

Three of 12 evaluable patients (25%) completed the entire 6 cycle chemotherapy regimen with no infections. Nine patients (75%) developed a grade 3 bacterial infection, and six of these infections occurred during cycles when no prophylactic growth factor was administered. (Figure 2) There were no grade 4 infections and no patients required intensive care treatment or died from infection. There were no fungal infections. No patient had more than one infection. Four infections (44%) were bacteremia (Staphylococcus aureus- 2, Staphylococcus epidermidis- 1, Streptococcus mitis- 1), three (33%) were skin/soft tissue infections, and two (22%) were urinary tract infections (Escherichia Coli −1, Pseudomonas aeruginosa- 1). Two infections (urinary tract infection, bacteremia) occurred while receiving high dose G-CSF for stem cell mobilization. One infection (skin/soft tissue) occurred during cycle 5 while receiving GM-CSFprior to surgical resection. There were no post-operative infections.

Febrile Neutropenia

Febrile neutropenia without a bacterial or fungal infection identified occurred in 21 out of the 58 cycles completed on study (36%). The eight patients who completed all 6 cycles of induction chemotherapy on study experienced a median of 2(range of 0 to 4) episodes of febrile neutropenia. One patient completed therapy with no episodes of febrile neutropenia or infection.

Delays in chemotherapy administration due to neutropenia

Eightchemotherapy cycles (14%)in5 patients were delayed beyond 22 days from initiation of prior chemotherapy cycle due to neutropenia with ANC<750. In six cases, the patient’s ANC met criteria for administration of chemotherapy within 29 days from the prior cycle, and in two cases by day 36.There were two delays following each of cycles 1-4. Six delays occurred following cycles when no growth factors were administered, and two delays occurred following growth factor administration.

Response to induction chemotherapy

Eight patients completed all 6 cycles of induction chemotherapy on study and were evaluable for the response endpoint. Four patients had complete responses, two had very good partial responses and two had partial responses.

Discussion

The goal of this study was to determine whether prophylactic G-CSF can be eliminated during induction chemotherapy for HR-NBL without increasingthe rate of serious bacterial or fungal infections. We observed grade 3 bacterial infections inmore patients than predicted, which did not support our model for reducing G-CSF administration during induction chemotherapy.

Prior studies comparing the use of primary prophylactic G-CSF in HR-NBL consistently demonstrated a reduction in the period of severe neutropenia when primary prophylactic G-CSF was administered.[6–8] However, no study has demonstrated a reduction in serious bacterial infections in children with high-risk neuroblastoma with the use of G-CSF. A randomized comparison of the Society of Pediatric Oncology Europe Neuroblastoma Group's (SIOPEN) standard rapid COJEC regimen (8 cycles of combinations of vincristine, carboplatin, etoposide, cyclophosphamide and cisplatin), with or without primary prophylactic G-CSFdemonstrated a modest reduction in risk of infection with G-CSF administration.However, this reduction was only found in mild infections with no difference in risk of serious infection requiring intravenous antibiotics.[8] A separatestudy showed no difference in febrile episodes or incidence of infections when patients who received primary prophylactic G-CSF were compared to historical controls who had received the same chemotherapy regimen without G-CSF.The study did confirm that G-CSF exposed patients experienced a shorter duration of neutropenia, but also experienced an increase in duration of thrombocytopenia leading the authors to concludethat G-CSF use did not impact dose intensity due to delays in platelet recovery.[7]

As noted, aneuroblastoma CSC, defined by expression of the G-CSF receptor (CD114), expands both *in vitro* and *in vivo* after exposure to exogenous G-CSF, leading to enhanced tumor growth and metastasis in xenograft and murine neuroblastoma models.[14–16] Although our study did not support the complete elimination of G-CSF as a primary prophylaxis, concerns about how exogenous G-CSFimpacts neuroblastoma CSCs remain.

Continued attempts to reduce exposure to G-CSFthrough other methods may be beneficial in neuroblastoma. While it is unlikely that exogenous myeloid growth factors can be eliminated, a reduction in exposure could be accomplished by reverting to daily injections of G-CSF stopping when ANC is rising rather than the less controlled use of pegylated G-CSF. Furthermore, administration of GM-CSF as a primary prophylactic growth factor could be considered.GM-CSF binds its own receptor, CD116, and does not bind to CD114. A prior randomized study demonstrated that GM-CSF led to a slower ANC recovery to above 1500/uL, but no difference in the rate of serious infections, antibiotic administration or length of hospitalization.[20] Furthermore, GM-CSF may have anti-tumor effect by enhancing cell-mediated cytotoxicity.[24] GM-CSF has been used as an adjuvant to immunotherapies in a variety of cancers including in combination with anti-GD2 antibody therapies in neuroblastoma.[24–27]

As data emerges on the effect of GM-CSF on the tumor microenvironment and enhanced cell-mediated toxicity, GM-CSF may be preferred over G-CSF as primary prophylaxis.

Further studies are needed to elucidate this potential benefit. In an ongoing Children's Oncology Group (COG) (NCT03786783) trial which incorporates the anti-GD2 dinutuximab into the standard chemotherapy induction, GM-CSF is used for both its cytokine effect as well as primary neutropenia prophylaxis. As the data from this trial matures, we may learn more about potential benefits of GM-CSF over G-CSF in induction treatment for patients with HR-NBL.

This study was designed to pilot a means to safely decrease exposure to G-CSF by eliminating its use for primary prophylaxis. To formally test the non-inferiority of not giving G-CSF a much larger sample size would be neededand our early pilot does not support such a study. This study does not conclude that G-CSF prevents infections, indeed two of the infections occurred during higher doses of G-CSF used for stem cell collection.

In summary, we observed anincreased incidence of serious bacterial infections compared to our historical cohortwhen prophylactic G-CSF was not administered during induction therapy for HR-NBL.Further assessment of the impact of hematopoietic cytokines on cancer stem cells and the tumor microenvironment is warranted, as tumor immune evasion is a critical barrier to cure, and immunotherapeutic modulation is rapidly becoming incorporated as standard of care for pediatric and adult malignancies.

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Abbreviations:

HR-NBL	High risk neuroblastoma
CSC	Cancer stem cell
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-monocyte colony stimulating factor
STAT3	Signal transducer and activator of transcription 3

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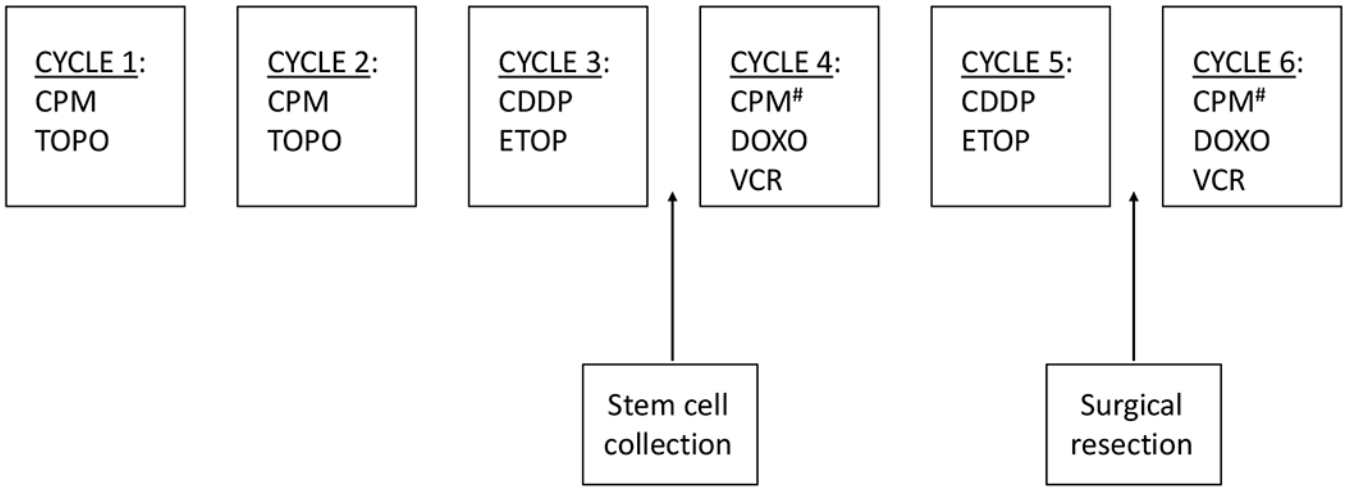

Figure 1.

CPM- cyclophosphamide 2000 mg/m^2 over 5 days, TOPO- topotecan 6 mg/m^2, CDDP-cisplatin 200 mg/m^2 over 4 days, ETOP- etoposide 600 mg/m^2 over 3 days, CPM$^{\#}$-cyclophosphamide 4200 mg/m^2 over 2 days with mesna, DOXO- doxorubicin 75 mg/m^2 over 3 days with dexrazoxane, VCR-vincristine 2 mg/m^2 over 3 days.

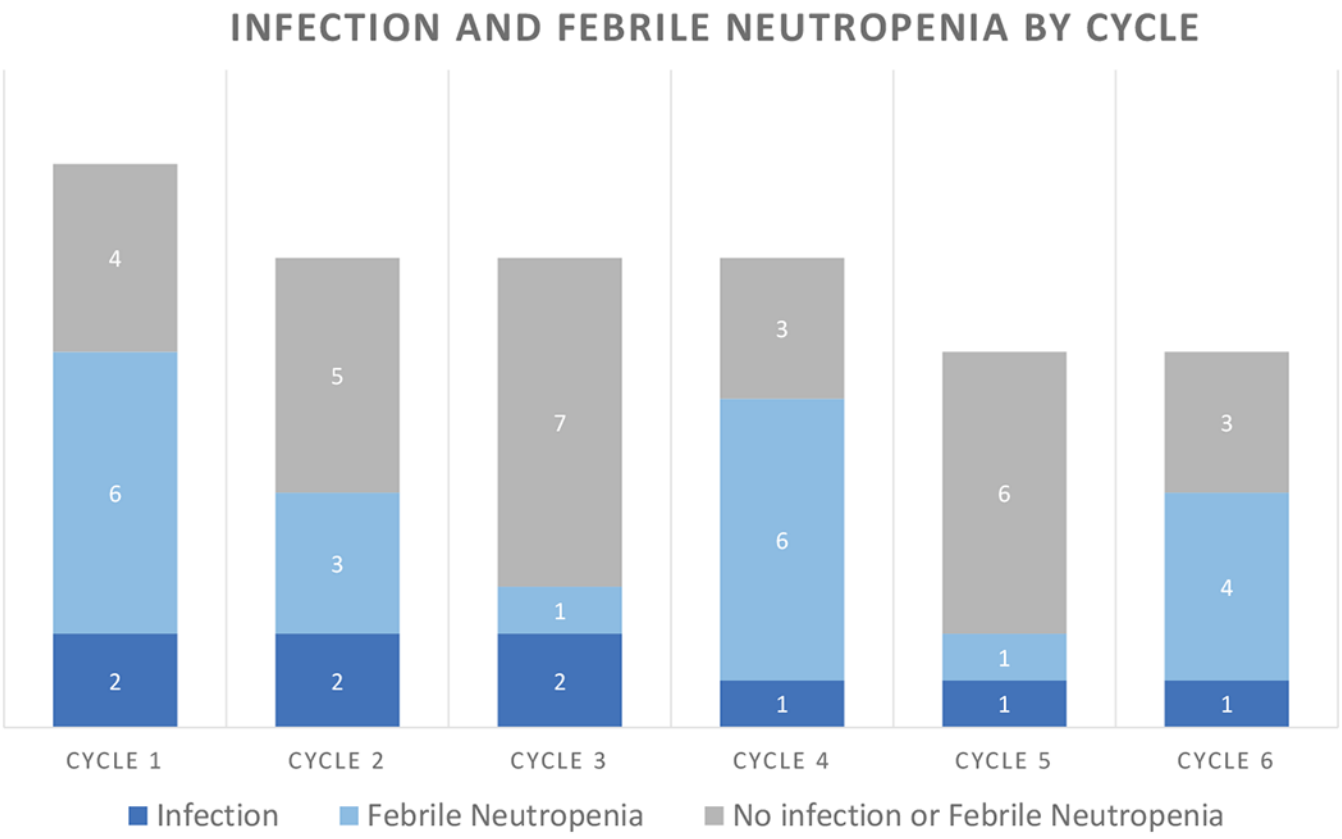

Figure 2.

Number of patients with infection, febrile neutropenia, or neither per cycle. G-CSF was administered to all patients in cycle 3 for stem cell collection and GM-CSF was administered to all patients after cycle 5 to facilitate scheduling for surgical resection.

Table 1:

Trial Participant Characteristics

Age	**Median = 2.9 years (34 months)**	**Range= (1.1-6.7 years)**
Demographic	**n**	**%**
Sex		
Male	8	67
Female	4	33
Race/Ethnicity		
NH White	8	67
NH Black	3	25
Asian/Pacific Islander	1	8
INRG Stage		
L2	2	17
M	10	83
MYCN amplification		
Yes	6	50
No	6	50
Bone Marrow involvement		
Yes	9	75
No	3	25

NH-Non-Hispanic, INRG – International Neuroblastoma Risk Group