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Blood Product Administration During High Risk Neuroblastoma Therapy

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Abstract

The increasing intensity of high-risk neuroblastoma (HR NB) treatment over the last decades has resulted in improved survival at the expense of prolonging therapy and exposure to additional potentially toxic agents. Anemia and thrombocytopenia requiring transfusion are common during therapy for HR NB. Risks of cumulative red blood cell and platelet transfusions are incompletely defined in pediatric oncology patients, however, risks of transfusional iron overload are well described in other populations. This study aimed to determine the number of packed red blood cell (pRBC) and platelet transfusions throughout treatment for HR NB and how these numbers have changed with modern therapy. We performed a retrospective review of 92 patients with HR NB from June 2002 until September 2017. Patients received a median of 20 pRBC and 32 platelet transfusions. Our results demonstrated large numbers of transfusions with significantly increased blood product exposures among patients who received intensified therapy, either with additional induction chemotherapy, tandem autologous stem cell transplants, or dinutuximab plus cytokines with isotretinoin. Similar volumes of pRBC transfusions have been associated with iron overload in other populations and warrant further discussion of guidelines for long-term follow up of HR NB patients.

Keywords

Neuroblastoma; Blood transfusions; Iron overload

Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood with a prevalence of one case per 7,000 live births.^{1,2} Nearly 90% of patients are diagnosed before the age of five.³ Over half of patients are found to have high-risk (HR) metastatic disease at

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Disclosure statement

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time of diagnosis with a five-year survival rate of 40-50%.⁴⁻⁶ Historically, therapy consisted of several cycles of chemotherapy, surgery to resect the primary tumor, and radiotherapy to the tumor bed and select metastatic sites. In recent decades, a series of clinical trials have demonstrated incremental improvements in survival with intensified and prolonged therapy, leading to a new standard treatment. Most modern therapy consists of the following three phases: (1) induction (multiple cycles of chemotherapy and primary tumor resection), (2) consolidation (single or tandem cycles of high-dose chemotherapy with autologous stem-cell rescue followed by radiation to the primary and remaining metastatic sites), and (3) maintenance (immunotherapy with dinutuximab, cytokines, and isotretinoin).^{4,5,7,8}

Patients with HR NB regularly require packed red blood cell (pRBC) and platelet transfusions as supportive care for anemia and thrombocytopenia. The causes of their cytopenias are multi-factorial, including bone marrow infiltration by NB, myelosuppression from chemotherapy or radiotherapy, decreased production from chronic disease, nutritional deficiencies, and blood loss.^{9,10} Clinical trials report on the frequency of cytopenias using the US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). This method of reporting, however, does not capture the frequency of blood product transfusions. Nor does CTCAE grading reflect symptomatology or institutional transfusion thresholds, making it impossible to determine the number of transfusions administered from these data.¹¹⁻¹³

The objective of this study was to determine the number of pRBC and platelet transfusions throughout the course of treatment for HR NB and to estimate how this may have changed in the era of modern treatment.

Materials and Methods

Patient population

This study was approved by the Baylor College of Medicine Institutional Review Board. A retrospective review of electronic medical records was conducted for patients diagnosed with HR NB and treated at Texas Children's Hospital (TCH) from June 2002 until September 2017. Blood transfusion records were obtained from blood bank electronic records.

Patients were included in the study if they were considered to have HR NB at the time of their diagnosis and completed, at minimum, the entirety of induction chemotherapy at TCH. As the definition of HR disease has changed over time, we included patients who would now be classified as intermediate risk, as long as they were classified as HR and treated accordingly at time of diagnosis. Patients were excluded if they completed any portion of induction therapy outside of TCH or if they died during induction therapy. Patient data was included during the time of upfront therapy only and did not include data from relapsed disease treatment. Patients who received extended induction therapy secondary to poor induction response were included. Patient information was evaluated at the end of each phase of therapy—induction, consolidation, and maintenance—and included only if the patient remained on site for the entirety of that phase of therapy. As such, patients were included in the analysis for one to three phases in total. Information collected for each

patient included demographics, disease characteristics, treatment regimen, and number of pRBC and platelet transfusions.

During induction, patients received five to six cycles of chemotherapy and underwent tumor resection after which disease response was evaluated; for patients who did not respond adequately, they often received additional cycles of chemotherapy. During consolidation, patients either received single or tandem autologous stem cell transplant (ASCT) and radiation therapy. Single ASCT recipients received one of two conditioning regimens: carboplatin, etoposide and melphalan (CEM) or busulfan and melphalan (BuMel).^{4,14,15} Tandem ASCT recipients received conditioning with cyclophosphamide and thiotepea followed by modified CEM.⁷ Radiation was administered at a dose of 21.6 Gy in 12 fractions to the primary tumor bed and metastatic sites that remained post-induction. Patients who went on to maintenance therapy received either isotretinoin alone or isotretinoin in combination with dinutuximab, interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF).⁸

During the time period of this study, our institutional standard was to transfuse pRBCs if hemoglobin levels fell below 8 g/dL or if the patient had symptomatic anemia. During radiation therapy and prior to the start of each dinutuximab course, pRBCs were transfused if the hemoglobin fell below 10 g/dL. This increased threshold was used to prevent hypotension and capillary leak during dinutuximab and cytokine infusions and to limit tumor hypoxia during radiation therapy.¹⁶ Each pRBC transfusion was assumed to be our institution's standard of 10 ml/kg of volume. Platelets were transfused if levels fell below $20 \times 10^9/L$ or for bleeding symptoms. Platelet transfusion volumes were not analyzed as the institutional standard varied during the study time.

Statistical Analysis

Tests for statistical analyses were performed using the Mann-Whitney U test. Data was first analyzed as an entire group, looking at total pRBC and platelet transfusions. It was then subdivided to identify the number of transfusions by (1) each individual phase of therapy (induction, consolidation, maintenance) and (2) further stratified by differences within each phase: induction chemotherapy alone versus extra chemotherapy prior to consolidation due to inadequate disease response; single versus tandem ASCT during consolidation; isotretinoin alone versus isotretinoin plus dinutuximab and cytokines during maintenance. All analyses were performed in SPSS 2017 Version 25.0 (IBM, New York) and considered significant if p-values for two-sided tests were <0.05 .

Results

Patient demographics are listed in Table 1. Ninety-two patients met inclusion criteria. The average age at time of diagnosis was 3.62 years old (min 0.18 years, max 17.65 years). The majority of patients were male, and white was the most commonly identified ethnicity. At the time of diagnosis, 64% of patients had bone marrow involvement. *MYC*-N amplification was present in 57% of patients. For the 48 patients who completed maintenance therapy, the average length of therapy—as defined by date of diagnosis until the date that maintenance was completed—was 1.26 years.

During induction, 17% of patients required additional chemotherapy prior to proceeding to consolidation secondary to poor disease response. For consolidation, 69% received a single ASCT; 14% of those patients received BuMel and the remainder received CEM. Among the cohort eligible for maintenance therapy, 69% received isotretinoin alone and 31% received dinutuximab and cytokines in addition to isotretinoin.

Transfusion Burden

A median of 12 pRBC (range 1-41) and 8.5 platelet (range 0-113) transfusions per patient were given during induction, 6 pRBC (range 0-27) and 17 platelet (range 2-156) transfusions during consolidation, and 0 pRBC (range 0-9) and 0 platelets (range 0-4) during maintenance. Patients who completed the entirety of standard therapy for HR NB received a median of 20 (range 4-41) pRBC transfusions and 32 (range 3-125) platelet transfusions in total. Among the cohort who were included for all three phases of therapy, the total number of pRBC transfusions was a median of 17 for those who received isotretinoin alone as maintenance therapy and 23 for those who received isotretinoin with dinutuximab and cytokines.

Considering each phase of treatment individually (Table 2), those who received additional rounds of chemotherapy after standard induction received significantly more pRBC and platelet transfusions during induction ($p = 0.001$ and 0.035 , respectively). During consolidation, those who received tandem ASCTs received significantly greater numbers of platelet transfusions than those who underwent single ASCT ($p = 0.003$); the number of pRBC transfusions was not significantly different ($p = 0.155$). During maintenance, those who received dinutuximab and cytokine therapy in addition to isotretinoin received significantly more of both pRBC and platelet transfusions ($p < 0.001$ and $p = 0.004$, respectively).

We next analyzed the cohort of 48 patients who completed all three phases of therapy and found there was no significant difference in the overall treatment total number of pRBCs or platelets transfused for those who received additional chemotherapy during induction ($p = 0.104$ and 0.876 , respectively). Within this group, there was also no difference in total pRBC transfusions for those receiving tandem versus single ASCTs ($p = 0.500$); there was a significant increase in platelet transfusions ($p = 0.013$). Finally, patients who received maintenance with dinutuximab and cytokine therapy in addition to isotretinoin received significantly greater numbers of pRBC transfusions throughout their therapy ($p = 0.015$), but fewer platelet transfusions ($p = 0.043$). The difference in number of pRBC transfusions among those with isotretinoin alone versus intensified maintenance therapy is depicted in Figure 1.

Discussion

This study describes the exposure to pRBC and platelet transfusions during upfront therapy for patients with HR NB. Patients who completed all phases of therapy received a median of 20 pRBC transfusions and 32 platelet transfusions. As expected, our results demonstrated significantly increased blood product exposures among patients who received more intensive therapy, either with additional induction chemotherapy, tandem ASCT, or dinutuximab plus

cytokines with isotretinoin. Importantly, we demonstrated that addition of dinutuximab and cytokines to maintenance chemotherapy significantly increased exposure to pRBC transfusions. While there was no significant difference in total pRBC transfusions for those receiving tandem versus single ASCTs, this may change as additional patients are treated with tandem transplant.

These results show that as therapy has intensified over time, so too have exposures to blood products. Blood product transfusions carry several medical and non-medical risks. Increases in transfusion requirements likely lead to additional or longer clinic visits, hospitalizations, and emergency room visits, all of which contribute to the burden of diagnosis to a family including time away from work, school and home, and costs to both the family and medical system. Medical risks of transfusion include acute risks such as transfusion reactions, viral and bacterial infections, and chronic risks including immune injury and modulation and transfusional iron overload.^{9,17-19} While little is known regarding long-term effects from platelet transfusions, repeated red blood cell transfusions are known to cause iron overload.^{9,18}

Numerous studies describe iron overload among patients with transfusion-dependent thalassemia and sickle cell disease, however, far less is known about the implications of transfusional iron overload in childhood cancer survivors.²⁰ Among survivors, as few as ten transfusions have been repeatedly shown to lead to iron deposition in the liver, heart, skin and endocrine organs,^{9,21-23} and may lead to hepatic fibrosis, cirrhosis, hepatocellular carcinoma, and cardiac dysfunction.^{21,22} Several studies describe the risk for iron overload increasing in proportion to the total number or volume of pRBC transfusions received.^{21,22,24-27} Such studies have described a wide range of iron overload prevalence in childhood cancer survivors – as commonly measured by serum ferritin or hepatic and cardiac T2* MRI. However, direct comparisons are challenging because the definition of iron overload varies between studies as do patient populations and timing of the measurements in relation to therapy. Studies reviewing patients with hematologic malignancies and solid tumors have shown ranges of general iron overload as low as 2.6%, measured by elevated ferritin,²⁶ to 49% and 66% with liver iron overload and 0% to 14% with myocardial iron overload, measured by hepatic and cardiac T2* MRI.^{21,22} Studies focusing on patients with acute lymphoblastic leukemia (ALL) describe anywhere from 63% of liver iron overload towards the end or at the end of therapy and 14% with persistent overload off therapy, as defined by iron deposition on liver biopsy;²⁴ a cohort of patients with ALL both during and following therapy found 50% with hepatic iron loading and 27% with cardiac iron loading by T2* MRI.²⁷ Finally, one study assessing serum ferritin levels in cancer patients with a history of allogeneic HSCT found iron overload in 26% of patients compared to 3.7% in those without HSCT and 0% among those with autologous HSCT.²⁵ Ultimately, while heterogeneous in content, this literature uniformly highlights the importance of using the known risk of iron overload among childhood cancer survivors to establish appropriate and adequate screening for long term effects.

Although some of these studies did include patients with HR NB, numbers are too small to draw any conclusions specific to this population, and existing studies of HR NB late effects have not focused on the role of iron overload, if any, in this population.^{28,29} Current

Children's Oncology Group (COG) long-term follow up guidelines recommend screening for iron overload in children post hematopoietic stem cell transplant (HSCT) using ferritin.³⁰ The guidelines do not differentiate monitoring for allogeneic versus autologous stem cell transplants and lack specificity regarding frequency and timing of follow up measurements or interventions in the event of an elevated ferritin measurement. While HR NB patients fall within the COG guidelines to screen for iron overload post ASCT, the frequency and consequences of iron overload in this population have not been determined. Our study demonstrates that intensification of maintenance therapy to include dinutuximab with cytokines may increase the potential for iron overload in modern survivors of HR NB and suggests that further studies specifically addressing iron overload in HR NB survivors are warranted.

Further, care in determining necessity of pRBC transfusions is important to help limit overall numbers of transfusions. For those who frequently fall below the transfusion threshold, consideration of symptoms such as tachycardia or dizziness may guide clinical care. During the period of this study, our institution routinely transfused pRBCs for hemoglobin below 8 g/dL. More recent reviews suggest a lower threshold of 7 g/dL is safe for asymptomatic anemia in oncology patients. These studies demonstrate that adopting a lower tolerated hemoglobin threshold for asymptomatic patients limits the risk of exposure to blood products and their associated complications and are well tolerated amongst patients.^{31,32}

Limitations of this study include that it is a single center retrospective data collection with a limited sample size. Due to our small sample size, we are not able to comment on any possible confounding relationship between those who received intensified induction chemotherapy and potential for more intensive consolidation or maintenance. Our institutional guidelines during the time period in this study recommended a transfusion for platelet counts less than $20 \times 10^9/L$ or bleeding symptoms and transfusion of pRBCs for hemoglobin less than 8 g/dL, except for a goal of 10 g/dL during radiation and on the first day of each dinutuximab course to mitigate capillary leak. These guidelines may not have been used at other centers, potentially limiting the generalizability of our data with respect to specific numbers of transfusions administered. However, the trend toward increased exposure to blood products with intensified therapy is likely to apply broadly. Newer evidence-based guidelines have since been implemented in our institution to lower the pRBC transfusion threshold to hemoglobin of less than 7g/dL.^{31,32} We elected to use number of transfusions as the focus of this study and not frequency and degree of cytopenias as transfusion administration is often individualized to address a patient's clinical status. Additionally, our study focused on the administration of pRBC and platelet transfusions only as these are the most commonly administered products. We chose not to focus on other blood products such as fresh frozen plasma or granulocytes given the rarity of these infusions in our patients. Finally, we were unable to directly study the incidence or consequences of iron overload in our population as our institution has not been systematically screening for iron overload with ferritin levels or by alternate means.

In summary, our data demonstrate that survivors of modern era treatment for HR NB have received a large number of transfusions of both pRBCs and platelets. These patients are at

risk for acute and chronic complications of transfusions. In particular, they are at risk for iron overload, likely to a higher degree than HR NB survivors studied prior to the addition of dinutuximab to standard treatment. Detailed transfusion histories should be a standard part of follow-up care for survivors of HR NB to identify those at highest risk of iron overload to enable targeted screening. Additionally, iron overload and its consequences should be reported in future studies of late effects in HR NB survivors.

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Figure 1. Total number of pRBC transfusions during entirety of therapy, stratified by maintenance regimen ($p = 0.015$).

Table 1.

Demographics.

n (%)	
Gender	
Male	55 (59.8)
Female	37 (40.2)
Race	
White	57 (62.0)
Black	15 (16.3)
Hispanic	10 (10.9)
Asian	5 (5.4)
Unknown	5 (5.4)
Stage at Diagnosis	
3	9 (9.8)
4	80 (87.0)
4S	2 (2.2)
Unknown	1 (1.1)
Bone Marrow Involvement?	
Yes	59 (64.1)
No	33 (35.9)
MYC-N Amplification Status	
Amplified	52 (56.5)
Not Amplified	36 (39.1)
Unknown	4 (4.4)
Phase of Therapy Completed	
Induction	92 (100)
Consolidation	74 (80.4)
Maintenance	48 (52.2)

Table 2.

Median (min, max) pRBC and platelet transfusions during each phase of therapy.

Induction	Induction alone	Induction + extra chemo	p-value
	<i>n</i> = 76	<i>n</i> = 16	
pRBCs	11 (1-25)	17 (8-41)	0.001
platelets	8 (0-56)	11.5 (5-113)	0.035
Consolidation	Single ASCT	Tandem ASCT	p-value
	<i>n</i> = 51	<i>n</i> = 23	
pRBCs	5 (0-27)	6 (4-12)	0.155
platelets	14 (0-156)	28 (7-81)	0.003
Maintenance	Isotretinoin alone	Isotretinoin + dinutuximab & cytokines	p-value
	<i>n</i> = 33	<i>n</i> = 15	
pRBCs	0 (0-9)	6 (2-9)	0.000
platelets	0 (0-4)	0 (0-4)	0.004