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ORIGINAL ARTICLE

Anemia and Bone Marrow Suppression after Intra-Arterial Chemotherapy in Children with Retinoblastoma

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ABSTRACT

Background: Intra-arterial chemotherapy (IAC) has become a vital treatment approach for retinoblastoma, particularly in cases where other therapies have failed.
Objective: This study investigates the incidence, severity, and factors influencing anemia and bone marrow suppression in children with retinoblastoma undergoing IAC.
Methods: This retrospective study was conducted at Pediatrics Department, Swat Medical College & Swat Medical Complex Teaching Hospital Saidu Sharif Swat during January 2024 to August 2024. A total of 185 pediatric patients who underwent IAC treatment for retinoblastoma were included in this study. Patients aged 0 to 18 years who had received at least one cycle of IAC as part of their treatment regimen for retinoblastoma were included in the study. Patients who had incomplete medical records or were lost to follow-up were excluded from the study.
Results: The incidence of anemia increased from 10% before IAC to 65% after treatment. Bone marrow suppression was observed in 55% of patients, with severe neutropenia and thrombocytopenia occurring in 15% and 10%, respectively. The number of IAC cycles (≥5) and the dose of melphalan were significant predictors of anemia and bone marrow suppression severity ($p < 0.01$). Advanced-stage disease was also associated with a higher risk of severe hematologic toxicity ($p < 0.05$). Supportive care interventions, such as blood transfusions and granulocyte colony-stimulating factor (G-CSF), were effective in managing these complications.
Conclusions: Anemia and bone marrow suppression are common complications in children with retinoblastoma undergoing IAC.
Keywords: Retinoblastoma, Intra-arterial Chemotherapy (IAC), Anemia, Bone Marrow Suppression, Pediatric Oncology.

INTRODUCTION

Retinoblastoma (RB) is a rare and highly malignant tumor of the retina, affecting primarily infants and young children. It is the most common intraocular cancer in children, with an estimated incidence of 1 in 15,000 live births[1]. Early detection and treatment are crucial to prevent metastasis and preserve vision, as retinoblastoma can rapidly spread to the optic nerve, brain, and other parts of the body if left untreated. The vast majority of cases involve unilateral disease, although approximately one-quarter of cases are bilateral, which presents additional challenges in treatment and prognosis[2]. Over the past few decades, advancements in treatment strategies for retinoblastoma have substantially improved survival rates, with modern therapies providing an opportunity to preserve the globe in many children. One such treatment modality is intra-arterial chemotherapy

(IAC), a targeted approach that allows for higher concentrations of chemotherapy drugs to be delivered directly to the tumor through the ophthalmic artery[3]. Intra-arterial chemotherapy has revolutionized the treatment of retinoblastoma, offering a more precise and localized method of drug delivery compared to systemic chemotherapy. This technique, which is typically employed when other conventional treatments such as systemic chemotherapy, external beam radiation, or laser therapy have not been effective, targets the retinal tumor while sparing surrounding healthy tissue[4]. It has demonstrated remarkable success in reducing the need for enucleation (eye removal), allowing a significant number of children with retinoblastoma to maintain their vision. However, while the localized nature of IAC minimizes the systemic toxicity traditionally seen with chemotherapy, it is not without its complications[5].

Anemia and bone marrow suppression are two of the most frequently observed hematologic side effects in children undergoing intra-arterial chemotherapy for retinoblastoma. These conditions are both caused by the toxic effects of chemotherapy drugs on the rapidly dividing cells of the bone marrow, which is responsible for producing red blood cells, white blood cells, and platelets[6]. Anemia occurs when there is a deficiency in the number or function of red blood cells, leading to decreased oxygen delivery to tissues, which results in fatigue, weakness, and pallor. Bone marrow suppression, on the other hand, is a condition where the production of all blood cells is impaired, leaving the body vulnerable to infection, bleeding, and further complications[7]. Bone marrow suppression is a particularly concerning side effect because it can affect multiple blood lineages simultaneously, further exacerbating the clinical risks of chemotherapy. The occurrence of anemia and bone marrow suppression in children receiving intra-arterial chemotherapy for retinoblastoma varies based on several factors, including the dose and type of chemotherapy agents used, the number of treatment cycles, the underlying health of the child, and the child's age. Chemotherapy drugs such as melphalan, which is commonly used in IAC, are known to cause dose-dependent toxicity to the bone marrow[8]. Studies have demonstrated that even localized treatments can have significant hematologic adverse effects in some patients, despite the fact that the localized nature of IAC reduces the exposure of the bone marrow to these agents in comparison to systemic chemotherapy. Young children, whose bone marrow may be more susceptible to the toxic effects of chemotherapy, may find this to be particularly challenging[9]. The impact of anemia and bone marrow suppression on the clinical course and quality of life of children with retinoblastoma cannot be underestimated. In addition to the immediate hematologic risks, these complications can also influence the overall effectiveness of the retinoblastoma treatment regimen. For example, bone marrow suppression can lead to delays in subsequent chemotherapy cycles or reductions in dose intensity, which may negatively affect treatment outcomes[10]. Moreover, prolonged anemia can result in persistent fatigue, which further diminishes a child's quality of life, making it difficult to engage in normal daily activities[11]. Despite the importance of understanding and managing these complications, there is limited research focusing specifically on anemia and bone marrow suppression following intra-arterial chemotherapy for retinoblastoma. The majority of studies on retinoblastoma hematologic complications have focused on external beam radiation or systemic chemotherapy, with IAC's unique effects receiving relatively little attention. This gap in the literature highlights the need for further investigation into the hematologic toxicity associated with IAC and its impact on treatment outcomes[12].

Objective

This study investigates the incidence, severity, and factors influencing anemia and bone marrow suppression in children with retinoblastoma undergoing IAC.

METHODOLOGY

This retrospective study was conducted at Pediatrics Department, Swat Medical College & Swat Medical Complex Teaching Hospital Saidu Sharif Swat during January 2024 to August 2024. A total of 185 pediatric patients who underwent IAC treatment for retinoblastoma were included in this study. Patients aged 0 to 18 years who had received at least one cycle of IAC as part of their treatment regimen for retinoblastoma were included in the study. Patients who had incomplete medical records or were lost to follow-up were excluded from the study. Ethical approval for the study was obtained from the Institutional Review Board (IRB), and informed consent was provided by the parents or guardians of all participants.

Data collection

Data were retrospectively collected from the patients' medical records, including information on demographic characteristics, clinical presentation, treatment protocols, and outcomes. Patients were classified according to their disease stage at presentation: 47% had early-stage disease (Group A and B based on the International Retinoblastoma Staging System), while 53% had advanced-stage disease (Group C and D). The median

number of IAC cycles administered was 4 (range: 1 to 8), and the chemotherapy regimen typically involved the use of melphalan as the primary agent, either alone or in combination with other drugs such as topotecan. The decision to proceed with IAC was made by a multidisciplinary team of pediatric oncologists, ophthalmologists, and radiologists, based on tumor size, location, and the patient's overall health status. Data included the number of IAC cycles administered, the type and dosage of chemotherapy agents used, the occurrence of hematologic complications (specifically anemia and bone marrow suppression), and any interventions required to manage these complications. Hematologic parameters were routinely monitored during and after each chemotherapy cycle. Blood samples were collected for complete blood count (CBC) and differential at baseline, during each chemotherapy cycle, and at regular follow-up visits after treatment. Anemia was defined as a hemoglobin level of less than 11 g/dL for children aged 1 to 5 years and less than 12 g/dL for children older than 5 years. Bone marrow suppression was diagnosed based on a reduction in one or more blood cell lineages (red blood cells, white blood cells, or platelets) below the established reference ranges for age. The primary outcomes of the study were the incidence and severity of anemia and bone marrow suppression in the cohort. Secondary outcomes included the duration of hematologic complications, the need for blood transfusions, and the impact of these complications on subsequent chemotherapy cycles and overall treatment outcomes. Additionally, the study assessed the relationship between various factors, including patient age, gender, disease stage, number of chemotherapy cycles, and chemotherapy regimen, with the incidence and severity of hematologic adverse effects.

Data analysis

Data were analyzed using SPSS v17. Descriptive statistics, including mean, median, and standard deviation, were used to summarize patient demographics and treatment data. The chi-square test was employed to assess the association between categorical variables (such as gender and disease stage) and the occurrence of anemia or bone marrow suppression. Statistical significance was set at $p < 0.05$.

RESULTS

Data were collected from 185 patients, with a mean age of 3.2 ± 1.98 years (range: 0.5 to 6). Of these, 102 were male and 83 were female. Sixty percent had unilateral disease, while 40% had bilateral disease. Disease stage distribution showed 47% of patients had early-stage (Group A & B) and 53% had advanced-stage (Group C & D) retinoblastoma. The mean number of intra-arterial chemotherapy (IAC) cycles administered was 4 (range: 1–8), with melphalan being the most commonly used chemotherapy agent, followed by topotecan.

The study revealed that 65% of patients (120 out of 185) experienced anemia, with 30% requiring blood transfusions, and the incidence was statistically significant ($p < 0.05$). Bone marrow suppression occurred in 55% of patients (102 out of 185), with 18% requiring granulocyte colony-stimulating factor (G-CSF) and 6% needing platelet transfusions, showing statistical significance ($p < 0.01$). Severe neutropenia (WBC < 500/µL) affected 15% (28 patients), with G-CSF administered, while severe thrombocytopenia (platelets < 20,000/µL) was observed in 10% (18 patients), requiring platelet transfusions.

Anemia rose from 10% (18 patients) before IAC to 65% (120 patients) after IAC, with a statistical significance of $p < 0.01$. Severe anemia (hemoglobin < 7 g/dL) increased from 2% (4 patients) to 30% (55 patients), with $p < 0.05$. Bone marrow suppression increased dramatically from 5% (9 patients) to 55% (102 patients), with $p < 0.01$. Severe neutropenia (WBC < 500/µL) was observed in 1% (2 patients) before IAC and 15% (28 patients) after IAC ($p < 0.05$). Severe thrombocytopenia (platelets < 20,000/µL) was seen in 0% (0 patients) before IAC and 10% (18 patients) after IAC, with a statistical significance of $p < 0.05$.

The univariate regression analysis indicated that the number of intra-arterial chemotherapy (IAC) cycles (≥5) and the melphalan dose (high vs low) were significantly associated with both anemia severity and bone marrow suppression severity. The β coefficients for anemia and bone marrow suppression severity were 0.35 and 0.42 for the number of cycles, and 0.40 and 0.38 for the melphalan dose, respectively, with p-values < 0.01. Disease stage (advanced vs early) was also a significant predictor, with β coefficients of 0.30 for anemia and 0.28 for bone marrow suppression, and $p < 0.05$.

Table 1: Demographic and Baseline Characteristics of Study Cohort

Characteristic	Value
Total Number of Patients (n)	185
Mean Age (years)	3.2±1.98 (Range: 0.5 - 6)
Gender (Male/Female)	102/83
Unilateral Disease (%)	60%
Bilateral Disease (%)	40%
Disease Stage	
- Early Stage (Group A & B)	47%
- Advanced Stage (Group C & D)	53%
Mean Number of IAC Cycles	4 (Range: 1–8)
Chemotherapy Agents Used	Melphalan (most common), Topotecan

Table 2: Hematologic Complications in Children with Retinoblastoma Receiving Intra-Arterial Chemotherapy

Complication Type	Incidence (%)	Patients Affected (n)	Treatment Required	Statistical Significance
Anemia	65%	120	Blood Transfusions (30%)	$p < 0.05$
Bone Marrow Suppression	55%	102	G-CSF (18%) / Platelet Transfusions (6%)	$p < 0.01$
Severe Neutropenia	15%	28	G-CSF	N/A
Severe Thrombocytopenia	10%	18	Platelet Transfusions	N/A
Treatment Delays/Adjustments	25%	46	Dose Adjustments or Delays	$p < 0.01$

Table 3: Anemia and Bone Marrow Suppression in Children with Retinoblastoma Before and After Intra-Arterial Chemotherapy (IAC)

Condition	Before IAC (n = 185)	After IAC (n = 185)	Statistical Significance
Anemia	10% (18 patients)	65% (120 patients)	$p < 0.01$
Hemoglobin < 7 g/dL	2% (4 patients)	30% (55 patients)	$p < 0.05$
Bone Marrow Suppression	5% (9 patients)	55% (102 patients)	$p < 0.01$
Severe Neutropenia (WBC < 500/µL)	1% (2 patients)	15% (28 patients)	$p < 0.05$
Severe Thrombocytopenia (Platelets < 20,000/µL)	0% (0 patients)	10% (18 patients)	$p < 0.05$

Table 4: Univariate Regression Analysis of Intra-Arterial Chemotherapy (IAC) Related to Anemia Severity and Degree of Bone Marrow Suppression.

Variable	Anemia Severity (β Coefficient)	Bone Marrow Suppression Severity (β Coefficient)	p-Value
Number of IAC Cycles (≥5)	0.35	0.42	$p < 0.01$
Melphalan Dose (High vs Low)	0.40	0.38	$p < 0.01$
Age (Years)	0.12	0.08	$p = 0.12$
Gender (Male vs Female)	0.05	0.07	$p = 0.45$
Disease Stage (Advanced vs Early)	0.30	0.28	$p < 0.05$

Table 5: Multivariate Regression Analysis of IAC Factors Influencing Anemia Severity and Bone Marrow Suppression Severity

Variable	Anemia Severity (β Coefficient)	Bone Marrow Suppression Severity (β Coefficient)	p-Value
Number of IAC Cycles (≥5)	0.32	0.40	$p < 0.01$
Melphalan Dose (High vs Low)	0.38	0.35	$p < 0.01$
Age (Years)	0.10	0.06	$p = 0.18$
Disease Stage (Advanced vs Early)	0.28	0.30	$p < 0.05$

The multivariate regression analysis showed that the number of intra-arterial chemotherapy (IAC) cycles (≥5) and the melphalan dose (high vs low) remained significant predictors of both anemia severity and bone marrow suppression severity. The β coefficients were 0.32 for anemia severity and 0.40 for bone marrow suppression severity associated with the number of cycles, and 0.38 and 0.35, respectively, for melphalan dose, with p-values < 0.01. Disease stage (advanced vs early) also had a significant association, with β coefficients of 0.28 for anemia and 0.30 for bone marrow suppression, and $p < 0.05$.

DISCUSSION

This study aimed to evaluate the incidence, severity, and clinical implications of anemia and bone marrow suppression in children with retinoblastoma undergoing intra-arterial chemotherapy (IAC). The results of this research shed light on the hematologic complications of IAC and emphasize the significance of managing these side effects to improve patient outcomes. In our cohort of 185 children with retinoblastoma, we observed a significant increase in the incidence of anemia and bone marrow suppression after the initiation of IAC. Prior to treatment, anemia was present in only 10% of patients, but this rose sharply to 65% after IAC[13]. The severity of anemia was also notable, with 30% of patients requiring blood transfusions due to symptomatic anemia (hemoglobin < 7 g/dL). These findings align with previous research that indicates chemotherapy-induced anemia as one of the most common side effects of treatment in pediatric oncology patients[14].

Bone marrow suppression was similarly prevalent, with 55% of patients experiencing some form of suppression post-IAC. Severe forms of bone marrow suppression, such as neutropenia (WBC < 500/µL) and thrombocytopenia (platelets < 20,000/µL), were also

observed in a significant proportion of the cohort, with 15% and 10% of patients affected, respectively. These findings are consistent with the expected hematologic toxicity seen with high-dose chemotherapy agents such as melphalan[15]. While the localized nature of IAC reduces systemic exposure to chemotherapy, the high doses delivered directly to the tumor site can still impact the bone marrow, especially in children with rapidly dividing hematopoietic cells. Our analysis identified several factors that significantly influenced the severity of anemia and bone marrow suppression[16]. The number of IAC cycles and the dose of melphalan were the most significant contributors to these complications. Patients who received five or more cycles of IAC were at a higher risk of both anemia and bone marrow suppression, which is consistent with the cumulative toxicity observed with multiple chemotherapy cycles. This finding highlights the importance of balancing the number of cycles needed for effective tumor control with the potential for hematologic toxicity[17].

The melphalan dose also showed a significant association with both anemia and bone marrow suppression. Higher doses of melphalan were more likely to cause severe hematologic complications, reflecting the known dose-dependent toxicity of this drug. These findings are consistent with previous studies that have reported a higher incidence of bone marrow suppression with increased melphalan dosage, suggesting that careful dose optimization is crucial in minimizing toxicity while ensuring adequate treatment efficacy. Supportive care interventions played a critical role in managing hematologic complications in this cohort. Blood transfusions were necessary for 30% of patients with severe anemia, and platelet transfusions were required for those with significant thrombocytopenia[18]. Multivariate regression analysis further reinforced these findings, showing that both factors remained significant even after controlling for confounding variables such as age and disease stage. Hematologic complications were also linked to advanced-stage disease (Groups C and D), highlighting the difficulties in treating patients with more extensive disease involvement[19]. While this study provides valuable insights, it is not without limitations. The retrospective nature of the analysis means that some data, particularly regarding the timing and management of complications, may have been incomplete. Additionally, this study was conducted at a single institution, which may limit the generalizability of the findings. Further multicenter, prospective studies are needed to confirm these results and explore potential strategies to mitigate hematologic toxicity.

CONCLUSION

It is concluded that anemia and bone marrow suppression are common and significant hematologic complications in children with retinoblastoma undergoing intra-arterial chemotherapy (IAC). The findings of this study indicate that the number of chemotherapy cycles and the dose of melphalan are key factors contributing to the severity of these complications. Higher numbers of IAC cycles and increased melphalan doses were associated with a greater incidence of both anemia and bone marrow suppression.

DECLARATION

Authors' Contribution:
All authors made an equal contribution to the study and approved the final manuscript. Conflict of Interest: No conflict of interest.

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