THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 1, p.91-94

CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE-INSTITUTION REPORT

Gizhlaryan M. S.[1,2], Mesrobian A.A.[1], Tamamyan G. N[1,2], Anastasiadi M. G.[1,2], Sahakyan L. S.[3], Krmoyan L.M.[1,2], Petrosyan M. T.[1,2], Melnichenko I. V.[1,2], Danelyan H. S.[1,2], Danielyan S. H.[3], Vagharshakyan L. H.[1,2]

[1] Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center After Prof. R.H. Yeolyan, Yerevan, Armenia

[3] Department of Pediatric Oncology and Hematology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

[3] Hematology Center after Prof. R.H. Yeolyan, Yerevan, Armenia

Received 15.12.2020; accepted for printing 15.12.2020

Abstract

Background: *Thrombocytopenia is one of the most common toxicities of chemotherapy, causing symptoms ranging from mild petechiae to debilitating bleeding. These effects can lead to treatment delay and discontinuation, which subsequently affects outcome. The data on chemotherapy-induced thrombocytopenia is scarce, especially from the developing world, and until now there is no consensus on the appropriate management of this complication.*

Aim: *The aim of this study was to evaluate chemotherapy-induced thrombocytopenia in pediatric patients with acute lymphoblastic leukemia.*

Methods: *Medical records of acute lymphoblastic leukemia patients who were diagnosed and treated in 2019 at the only center for pediatric hematologic and oncologic disorders in Armenia – the Pediatric Cancer and Blood Disorders Center of Armenia – were retrospectively reviewed.*

Results: *A total of 29 patients with acute lymphoblastic leukemia, who were subsequently treated with International BFM (Berlin, Frankfurt, Muenster) Study Group acute lymphoblastic leukemia IC BFM 2009 protocol and achieved remission, were included in the current study. 17 (58%) patients were males. The median age was 4.5y. and range, 18 months – 17 years. 5 patients had T-acute lymphoblastic leukemia and 24 patients, B-acute lymphoblastic leukemia. During induction therapy, 11 patients (38%) developed critical thrombocytopenia with platelet counts ranging from 21×10^3/L to 46×10^3/L. During consolidation therapy, 16 patients (55%) developed moderate thrombocytopenia, with platelet counts ranging from 70×10^3/L to 86×10^3/L and 6 (21%) patients had critical thrombocytopenia, with platelet counts ranging from 27×10^3/L to 36×10^3/L. During the re-induction phase of therapy, 21 (72%) patients developed critical chemotherapy-induced thrombocytopenia with platelet counts ranging from 13×10^3/L to 45×10^3/L. Isolated thrombocytopenia occurred in 3 (10%) of the patients. Thrombocytopenia was managed by platelet transfusion. The median (range) pre-transfusion platelet count was 10×10^9 /L (5×10^9 –13×10^9/L) and increased significantly post-transfusion to 22×10^9/L.*

Conclusions: *During the course of therapy the vast majority of patients with acute lymphoblastic leukemia developed clinically significant thrombocytopenia. Although our study is small and involves the cases from one year, it includes all the acute lymphoblastic leukemia patients treated in Armenia. The study clearly shows that chemotherapy-induced thrombocytopenia is a very common complication of acute lymphoblastic leukemia therapy and larger studies needed to explore these findings.*

Keywords: *acute lymphoblastic leukemia, chemotherapy-induced thrombocytopenia, CIT, acute lymphoblastic leukemia, ALL*

Address for Correspondence:

Mane S. Gizhlaryan
Yerevan State Medical University after Mkhitar Heratsi
Koryun 2, Yerevan, 0025, Armenia
Phone: (+374 94) 212822
Email: gizhlaryan.maneh@mail.ru

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. ALL is the most common form of cancer in children, com-

prising approximately 30% of all childhood malignancies. The treatment for the disease is focused on chemotherapy, which is known to cause various side effects. One of the predominant complications includes chemotherapy-induced thrombocytopenia **(**CIT)□ There are several reports which study the relationship between the incidence of CIT and different chemotherapy drug types. Similarly, research on the severity and risk factors of myelotoxicity associated with clinical features is limited. The existing studies primarily focus on solid tumors, however, the incidence of CIT in hematological tumors is reported to be as high as 75% [*Kantarjian H et al., 2007; Liou S et al., 2007*].

CIT is a common hematologic toxicity of myelosuppressive and ablative therapy [*Tamamyan G et al., 2016*]. CIT is often accompanied by a reduction of other blood products. The data on CIT is scarce, especially from the developing world, and until now, there is no consensus on the appropriate management of this complication. Severe or persistent CIT is known to cause a higher risk of life-threatening spontaneous hemorrhage. It can also become a reason to reduce the drug dosage and/or delay the treatment [*Tamamyan G et al., 2016*]. It may cause symptoms ranging from mild petechiae up to debilitating bleeding.

Thrombocytopenia is defined as a platelet count of less than 150×10^3 per μL [*Gauer R, Braun N, 2012*]. The definition of isolated thrombocytopenia is a platelet count of less than $150\times10^9/L$, without anemia **(**Hb >120 *g/L* for males and >110 *g/L* for females) and without leucopenia **(**white blood cell count $>4\times10^9/L$).

Based on the platelet count **(**PLT), thrombocytopenia is categorized into four grades. Grade 1 or Mild TP: 75-150×10 $^3/\mu L$; Grade 2 or Moderate TP: 50-75×10 $^3/\mu L$; Grade 3 or Severe TP: 25-50×10 $^3/\mu L$; Grade 4 or Critical TP < 25.000 μL. Patients with PLT counts greater than or equal to $50\times10^3/\mu L$ rarely have symptoms, PLT count of 30 - $50\times10^3/\mu L$ rarely manifests as purpura, PLT count of 10-$30\times10^3/\mu L$ may cause bleeding with minimal trauma, and a PLT count < 5×10^3 per μL may cause spontaneous bleeding and is defined as a hematological emergency **[***Gauer R, Braun N, 2012*].

This study aimed to evaluate CIT incidence in pediatric patients with acute lymphoblastic leukemia **(**ALL) in Armenia.

MATERIAL AND METHODS.

We retrospectively reviewed data on all ALL patients diagnosed and treated at the Pediatric Cancer and Blood Disorders Center of Armenia in 2019. A total of 29 patients with ALL, of standard risk group, who were treated as per ALL IC-BFM 2009 protocol and achieved complete remission were included in this study. The median age at diagnosis was 4.5 years, ranging between 1.5 – 17 years. Overall, 17 patients **(**58%) were males and 12 **(**42%) were female. Most of the patients **(**n=24) had B-ALL, while only 5 patients had T-ALL.

The standard risk criteria were as per ALL-IC BFM 2009 protocol:

1. Age ≥ 1 year – < 6 year,
2. Initial WBC < 20.000/μL,
3. Peripheral blood **(**PB) Day 8: < 1.000 blasts/μL,
4. Flow cytometry Minimal residual disease **(**FC MRD) < 0.1% or M1/ M2 marrow on day 15 and no M2/3 marrow on day 33.

Complete remission criteria were as follows:

1. M1 marrow: < 5% blasts with normal or only slightly decreased cellularity, i.e., with signs of recovering hemopoiesis,
2. No localized leukemic infiltrates/masses on clinical examination and/or by imaging studies,
3. No leukemic cells in the Cerebrospinal fluid **(**CSF) obtained by the therapeutic LP on day 33.

Patients with severe thrombocytopenia were managed by platelet transfusion at a platelet count of less than $10\times10^9/L$ in the absence of risk factors and at < $20\times10^9/L$ when risk factors were present **(**e.g fever, gum bleeding, bone marrow biopsy, lumbar puncture). Chemotherapy was not delayed because of isolated thrombocytopenia, but as a result of fever and neutropenia.

RESULTS

Ouf of the 29 patients with ALL who were analyzed, 11 patients **(**38%) developed critical thrombocytopenia with platelet **(**PLT) counts ranging from $21\times10^9/L$ to $46\times10^9/L$. During consolidation therapy, 16 patients **(**55%) devel-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

oped moderate thrombocytopenia with PLT counts ranging from $70\times10^9/L$ to $86\times10^9/L$ and 6 (21%) patients had critical thrombocytopenia with PLT counts ranging from $27\times10^9/L$ to $36\times10^9/L$. During the re-induction phase of therapy, 21 (72%) patients developed critical CIT with platelet counts ranging from $13\times10^9/L$ to $45\times10^9/L$. Isolated thrombocytopenia occurred in 3 (10%) of patients. Thrombocytopenia was managed by platelet transfusion. The median (range) pre-transfusion platelet count was 10×10^9 /L (5×10^9 –$13\times10^9/L$) and increased significantly to $22\times10^9/L$ post-transfusion.

Patients in the study group included in these clinical trials had mild clinical symptoms. Purpura and petechiae were found on the limbs, face and mouth. Clinical features mainly manifested with nosebleeds (epistaxis) and gum bleeding, which were managed by local hemostatic agents. Further bleeding, intracranial hemorrhage, and neurological symptoms have not been revealed. High fever > 38.0°C was observed mainly in the induction phase. Headache was manifested mainly in patients who have had severe anemia (Hb < 70 g/*L*).

Discussion

Acute lymphoblastic leukemia is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. It is also the most common pediatric malignancy, representing 75%-80% of acute leukemia among children (Samuel & Sakamoto, 2005). The main treatment for pediatric acute lymphocytic (lymphoblastic) leukemia (ALL) is chemotherapy, which is usually comprised of 3 main phases: induction, consolidation (also called intensification), and maintenance. Chemotherapy has side effects, one of which is CIT – a common hematologic toxicity of myelosuppressive and ablative therapy [*Tamamyan G et al., 2016*] Место для ввода текста.. The incidence and severity of CIT vary according to the type of chemotherapy drug. Not all chemotherapy drugs cause thrombocytopenia in the same way. The mechanism of thrombocytopenia varies according to therapeutic drugs; for example, alkylating chemotherapeutic drugs mainly affect multipotent stem cells [*McManus P, Weiss L, 1984*], cyclophosphamide mainly affects megakaryocyte progenitor cells. Ultimately, the fundamental cause of thrombocytopenia induced by chemotherapeutic drugs in normal doses is the underdevelopment of bone marrow megakaryocytes [*Zeuner A et al., 2007*].

There are several studies about CIT. One of the studies about prophylactic platelet transfusion in patients with hematologic malignancies has indicated that a prophylactic threshold of 10.000/L is generally well-tolerated and associated with a reduction in the platelet usage without increasing severe bleeding complications [*Benjamin R, Anderson K, 2002*]. Another recent study of the relationship between thrombocytopenia and bleeding in solid tumor patients showed that the incidence of bleeding doubled from 10% at a level below 20.000/L to 20% when the platelet count was below 10.000/*L* [*Vadhan-Raj, 2009*]. These results further indicate that a platelet count below 10.000/*L* is associated with an increased risk of bleeding [*Vadhan-Raj S, 2009*]. A guideline from the American Society of Clinical Oncology recommends a threshold of $10x10^9/L$ for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies [*Schiffer C et al., 2018*]. Transfusion at higher levels may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, rapid fall of platelet count, coagulation abnormalities (eg, acute promyelocytic leukemia), or undergoing invasive procedures. The same is advised for situations when platelet transfusions may not be readily available, as might be the case for patients who live at a distance from the treatment [*Schiffer C et al., 2018*].

In the current study, among patients with thrombocytopenia, bleeding increased as the platelet count decreased and platelet transfusions were the most effective and rapid treatment for patients with severe thrombocytopenia. Patients with severe thrombocytopenia were managed with platelet transfusion at a platelet count of $< 10\times10^9$ /L in the absence of risk factors and at $< 20\times10^9$ /L when risk factors were present (e.g fever, gum bleeding, bone marrow biopsy, lumbar puncture). Chemotherapy was not delayed because of isolated thrombocytopenia, but when fever and neutropenia occurred. However, we were not able to determine a specific threshold for a prophylactic platelet transfusion.

Analyzed data and the patient management did not differ from similar studies.

CONCLUSION

During the course of therapy, the vast majority of patients with ALL developed clinically significant thrombocytopenia. Although our study is small and involves the cases from one year, it includes all the ALL patients treated in Armenia. The study clearly shows that chemotherapy-induced thrombocytopenia is a very common complication of ALL therapy and larger studies are necessary to explore these findings.

REFERENCES

1. *Benjamin RJ, Anderson KC.* What is the proper threshold for platelet transfusion in patients with chemotherapy-induced thrombocytopenia? Critical Reviews in Oncology/Hematology. 2002; 42(2): 163-171
2. *Dezern AE, Petri M, Drachman DB, Kerr D, Hammond ER., et al.* High-dose cyclophosphamide without stem cell rescue in 207 patients with plastic anemia and other autoimmune diseases. Medicine. 2011; 90(2): 89-98
3. *Fitchen JH, Deregnaucourt J, Cline MJ.* An in vitro model of hematopoietic injury in chronic hypoplastic anemia. Cell Proliferation. 1981; 14(1): 85-90
4. *Gauer RL, Braun MM.* Thrombocytopenia. Am Fam Physician. 2012; 85(6): 612-622
5. *Kantarjian H, Giles F, List A, Lyons R, Sekeres MA., et al.* The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer. 2007; 109(9): 1705-1714
6. *Liou SY, Stephens JM, Carpiuc KT, Feng W, Botteman MF, Hay JW.* Economic burden of hematological adverse effects in cancer patients: A systematic review. Clinical Drug Investigation. 2007; 27(6): 381-396
7. *McManus PM, Weiss L.* Busulfan-induced chronic bone marrow failure: changes in cortical bone, marrow stromal cells, and adherent cell colonies. Blood. 1984; 64(5): 1036-1041
8. *Paramjit E, Rao R, Sudhamani S, Roplekar P, Shaffi Z, Roy S.* Spectrum of thrombocytopenia: A clinicopathological study with review of the literature. Muller Journal of Medical Sciences and Research. 2016; 7(2): 121
9. *Samuel ED, Sakamoto KM.* Topics in pediatric leukemia – acute lymphoblastic leukemia. MedGenMed: Medscape general medicine. 2021; 7(1): 23
10. *Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ., et al.* Platelet transfusion for patients with cancer. American society of clinical oncology clinical practice guideline update. Journal of Clinical Oncology. 2018; 36(3): 283-299
11. *Tamamyan G, Danielyan S, Lambert MP.* Chemotherapy induced thrombocytopenia in pediatric oncology. Critical Reviews in Oncology/ Hematology. 2016; 99: 29907
12. *Vadhan-Raj S.* Management of Chemotherapy-Induced Thrombocytopenia: Current Status of Thrombopoietic Agents. Seminars in Hematology. 2009; 46(2): S26-S32
13. *Zeuner A, Signore M, Martinetti D, Bartucci M, Peschle C, de Maria R.* Chemotherapy-induced thrombocytopenia derives from the selective death of megakaryocyte progenitors and can be rescued by stem cell factor. Cancer Research. 2007; 67(10): 4767-4773

THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 1

CONTENTS

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief
Fax: (+37410) 582532
E-mail: namj.ysmu@gmail.com, ysmi@mail.ru
URL: http//www.ysmu.am

Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "collage" LTD
Director: A. Muradyan
Armenia, 0002, Yerevan,
Saryan St., 4 Building, Area 2
Phone: (+374 10) 52 02 17,
E-mail: collageltd@gmail.com