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Evaluation of Possible Complications of Irradiation of Blood Products on Patients

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ABSTRACT

Background: Blood transfusion is a life-saving but high-risk procedure in various medical conditions as it is not a simple fluid infusion but an organ transplant. Although blood transfusions save lives, they may cause serious, life-threatening reactions. Nowadays, the number of reactions has decreased significantly with the reduction of leucocyte content of blood products or their irradiation.

Methods: A total of 5582 patients who received irradiated blood products in our hospital between 14/08/2020 and 17/02/2023 were included in the present study. Erythrocyte suspension, platelet apheresis, and pooled platelet suspension were irradiated at doses of 25–30 Gy.

Results: A total of 5582 blood products including 4990 erythrocyte suspensions, 282 pooled platelet suspensions, and 310 platelet apheresis were irradiated in the present study. No transfusion-associated Graft Versus Host Disease was identified in any patient included in the present study and there were only mild allergic reactions and febrile non-hemolytic transfusion reactions.

Conclusion: Based on the data obtained here from, it was concluded that irradiation of blood products can prevent the highly fatal transfusion-related Graft Versus Host Disease.

Keywords: Irradiated blood product, blood transfusion, reaction, transfusion-associated Graft Versus Host Disease

Etki altındaki hastalarda kan ürünlerinin ışınlamasının olası komplikasyonlarının değerlendirilmesi.

Süreç

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ÖZ

Amaç: Kan transfüzyonu, çeşitli tıbbi durumlarda hayat kurtarıcı, ancak yüksek riskli bir işlem olup basit bir sıvı infüzyonu değil, bir organ naklidir. Kan transfüzyonu hayat kurtarıcı olsa da hayati tehlikeye yol açan ciddi reaksiyonlara neden olabilir. Günümüzde, kan ürünlerinin lökosit içeriklerinin azaltılması ya da ışınlanması ile reaksiyon sayıları ciddi oranda azalmıştır.

Yöntemler: Çalışmamızda 14.08.2020 ile 17.02.2023 tarihleri arasında hastanemizde ışınlanmış kan ürünü alan toplam 5582 hasta dahil edildi. Eritrosit süspansiyonu, trombosit aferezi ve havuzlamış trombosit süspansiyonu 25-30 Gy'lik dozlar halinde ışınlanarak hastalara verildi.

Bulgular: Çalışmamızda 4990 eritrosit süspansiyonu, 282 havuzlanmış trombosit süspansiyonu, 310 trombosit aferezi olmak üzere toplam adet 5582 kan ürünü ışınlandı. Çalışmaya dahil edilen hiçbir hastada transfüzyon ilişkili Graft Versus Host Hastalığı saptanmamış olup, sadece hafif alerjik reaksiyon ve febril non-hemolitik transfüzyon reaksiyonları saptanmıştır.

Sonuç: Çalışmamızdan elde edilen veriler doğrultusunda, kan ürünlerinin ışınlanması ile son derece ölümcül olan transfüzyon ilişkili Graft Versus Host Hastalığının önlenebileceği sonucuna vardık.

Anahtar sözcükler: Işınlanmış kan ürünü, kan transfüzyonu, reaksiyon, transfüzyon ilişkili Graft Versus Host Hastalığı

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Introduction

Although blood transfusion represents a life-saving procedure in many cases, it may result in some early and late complications in patients with suppressed immune systems. Side effects that appear during or hours after transfusion are called as "early stage" reactions, while side effects that appear days, weeks, or years after transfusion are called as "late stage" reactions. Transfusion reactions can also be classified as immunological or non-immunological according to their mechanisms of manifestation [1]. Table 1 shows the classification of blood transfusion reactions.

Table 1: Blood transfusion reactions [1]

Reaction Type	Early	Late
Immune	Acute hemolytic transfusion reaction Febrile non-hemolytic transfusion reaction Urticaria, Anaphylaxis Transfusion-related acute lung injury	Delayed hemolytic transfusion reaction Transfusion-associated GVHD Post-transfusion purpura Immunomodulation
Non-immune	Transfusion-induced volume overload Hypothermia Hypotensive reactions Citrate toxicity Hyperkalemia Sepsis	Transfusion-transmitted infections Hemosiderosis

A rare complication of blood transfusion that can result in death with a mortality rate of 90% is transfusion-associated graft versus host disease (TA-GVHD) [2]. TA-GVHD is an immunological transfusion complication that develops when donor-derived lymphocytes attack the recipient's tissues. Donor blood that may initiate TA-GVHD despite the minimal concentration of lymphocytes is unknown; lymphocytes in the recipient as low as $1x10^4$/kg are sufficient to induce TA-GVHD [3]. TA-GVHD usually appears 4–30 days after transfusion. Skin rash, diarrhea, and worsening of liver function tests are followed by bone marrow hypoplasia and pancytopenia. In most blood transfusions, the immune system of the recipient destroys lymphocytes from the donor, and TA-GVHD never develops. However, if the recipient has immunodeficiency or if there is HLA compatibility between the recipient and donor, TA-GVHD may develop. For the precise diagnosis of TA-GVHD, it is necessary to biopsy the affected area and demonstrate donor-derived cells in the recipient tissues. The treatment of TA-GVHD includes immunosuppressant drugs such as corticosteroids, anti-thymocyte globulin (ATG), cyclosporine, methotrexate, and cyclophosphamide. But the utmost importance lies in preventing the development of TA-GVHD [4]. Irradiation of blood components using gamma or X-rays has been shown to prevent the proliferation of transfused lymphocytes in the recipient by inactivating lymphocytes through cross-linked DNA [5].

Blood products (whole blood, erythrocyte suspension, platelet suspension, and granulocyte suspension) to be transfused to patients at risk of TA-GVHD should be irradiated at a dose of 25 Gy. All recipients of cellular blood products from first- or second-degree relatives should receive them as irradiated, even if the recipient is immunocompetent. Table 2 shows the risk factors for 'TA-GVHD'.

Table 2: Risk factors for the development of TA GVHD[6]

High risk	Congenital immunodeficiency syndromes Autologous and allogeneic bone marrow transplantation Intrauterine transfusions HLA-matched platelet transfusion Hodgkin's disease Blood transfusion from a related donor Those treated with purine analogue drugs
Moderate risk	Acute leukemia Non-Hodgkin's lymphoma A solid tumor undergoing intensive chemotherapy or radiotherapy Blood transfusion in the newborn Prematurity Solid organ transplant recipients
Low risk	Healthy newborns Acquired immunodeficiency syndrome (AIDS)

Irradiation Dosage for Blood Products

To protect against TA-GVHD, blood products should be irradiated at doses between 1500 cGy and 5000 cGy. Doses above 1500 cGy are sufficient to prevent the development of TA-GVHD by destroying T lymphocytes. At doses above 5000 cGy, the functions and life span of erythrocytes, granulocytes, or platelets shorten [7]. The British Committee for Standards in Hematology (BCSH)

guideline recommends that blood products should be irradiated at least 2500 cGy, and no part of the product should be exposed to more than 5000 cGy [8]. The Association for the Advancement of Blood and Biotherapies (AABB) guideline recommends that the center of the product should be irradiated at least 2500 cGy and other parts of the product at least 1500 cGy [9]. The Japanese guideline recommends irradiation of the product between 1500 and 5000 cGy [10]. When any of those recommended doses are administered correctly, the development of TA-GVHD will be prevented.

MATERIALS AND METHODS

Irradiation Dosage for Blood Products

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Figure 1: GAMMACELL ELAN 3000 irradiator

Results

A total of 5582 patients, including 3093 males (55.4%) and 2489 females (44.6%) were included in the study. The mean age of the participants was 54.35±22.30 (min: 0 max: 95) years. The blood products (Erythrocyte suspension, pooled platelet suspension, and platelet apheresis) were transfused to the patients with the indication for irradiation hereunder. A total of 4990 of 36612 erythrocyte suspensions, 282 of 2123 pooled platelet suspensions, and 310 of 1722 platelet apheresis were irradiated during this period. A total of 5582 blood products were irradiated. The blood products were irradiated at blood irradiation centers at nominal doses of 25–30 Gy so that each region of the irradiated blood bags received a dose within ±5%.

When we analyzed the transfusion reactions of irradiated blood products, 7 of 4990 irradiated erythrocyte suspensions and only 4 of 310 irradiated platelet apheresis showed transfusion reactions, while no reaction was observed in 282 irradiated pooled platelet suspensions. Table 3 shows the distribution of irradiated and non-irradiated blood products. Table 4 shows the diagnoses of the patients included herein and irradiated blood products. Table 5 shows the number of reactions related to blood products. None of the patients included herein was diagnosed with TA-GVHD, but only mild allergic reactions and febrile non-hemolytic transfusion reactions were observed.

Table 3: Distribution of irradiated and non-irradiated blood products

Blood products	Irradiated	Not-irradiated
Erythrocyte suspension	4990	31622
Pooled Platelet Suspension	282	1840
Platelet apheresis	310	1412

Table 4: Diagnosis and irradiated blood products of the patients included in the study

Diagnosis	Erythrocyte suspension	Pooled Platelet Suspension	Platelet apheresis
Lung cancer	106	1	6
Brain cancer	37	1	-
Kidney cancer	10	-	-
Endometrial cancer	20	2	1
Multipl cancer	-	-	1
Liver cancer	15	1	1
Colon cancer	38	2	1
Breast cancer	18	-	-
Bladder cancer	17	-	3
Gastric cancer	203	17	11
Nasopharyngeal cancer	5	-	-
Esophageal cancer	6	-	1
Pancreatic cancer	2	-	-
Mesothelioma	7	-	1
Prostate cancer	59	5	4
Biliary tract cancer	12	-	1
Sarcoma	13	1	2
Testicular cancer	6	-	-
Acute lymphoblastic leukemia	192	4	18
Acute myeloid leukemia	949	48	75
Hodgkin lymphoma	28	3	3
Non- Hodgkin lymphoma	311	24	14
Chronic lymphocytic leukemia	283	13	18
Chronic Myeloid leukemia	33	1	4
Hairy cell leukemia	20	1	-
Multipl myelom	249	14	24
Aplastic anemia	176	13	10
Myelodysplastic syndrome	517	40	18
Myelofibrosis	447	25	18
Congenital neutropenia	3	-	-
ITP	30	1	6
Thrombocytopenia etiology	36	-	2
Premature	387	22	23
Newborn	5	-	-
Renal transplant	95	12	4
Liver transplant	2	-	-
Renal failure	79	4	8
Glomerulonephritis	17	-	-
Hemolytic anemia	66	7	2
Hemolytic uremic syndrome	18	4	-
HIV	7	-	-
Anemia etiology	76	-	-
Acquired Hemophilia	39	3	-
DIC	11	-	5
Thalassemias	77	-	-
Sickle cell anemia	13	1	-
Essential thrombocytosis	16	1	-
Multiple trauma	75	4	7
Pregnancy	14	-	1
Aortic dissection	16	-	2
Heart failure	6	-	-
Rheumatological diseases (RA+SLE+Wegener)	25	-	1
Crimean-Congo Hemorrhagic fever	10	-	7
Sepsis	11	-	2
Meningoencephalitis	19	2	1
Cerebrovascular infarction	8		
Other (child patient) (infection+epilepsy+trauma)	8	-	1
Other (adult patient)	40	6	3
Total	4990	282	310

ES: Erythrocyte suspension ITP: Immune thrombocytopenia, HIV: Human immunodeficiency virüs, DIC: disseminated intravascular coagulation, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus

Other (adult patient): Epidural bleeding, epilepsy, Fornier's gangrene, Glanzman's thrombasthenia, Huntington's chorea, drug intoxication, ileus, keratoacanthoma, pancreatitis, respiratory failure, ulcerative colitis, toxic epidermal necrolysis

Table 5: Reactions of blood products

Blood products	Total number of reactions	irradiated	Not irradiated
Erythrocyte suspension	47	7	40
Platelet apheresis	4	2	2
Pooled Platelet Suspension	1	0	1

Discussion

TA-GVHD is a complication of transfusion that is nearly invariably fatal, with a survival rate of less than 10% [11]. Currently, the approved method for the prevention of TA-GVHD involves the irradiation of cellular blood products using gamma rays or X-rays. TA-GVHD is highly complex to treat, but it is even more important to prevent it from developing in the first place. The best method for prevention under current conditions is the transfusion of blood products by irradiating them at appropriate doses to high-risk patients, as listed in Table 2.

Numerous previous studies have shown that the effect of irradiation on lymphocytes depends on the dose: 5 Gy eliminates lymphocyte proliferation, 15 Gy results in an 85% to 90% reduction in mitosis, and 50 Gy results in a 95% to 98.5% reduction [12, 13, 14]. Although a minimum dose of 15 Gy breaks DNA and prevents the proliferation of T-lymphocytes, the recommended dose for transfusion in the United States is 25 Gy to the center of the blood product bag (versus 50 Gy in some countries), and areas outside the center of the bag should receive a minimum of 15 Gy [15].

In their study, Kleinman et al., reviewed 12 published case reports and case series of TA-GVHD and concluded that irradiation of blood components using gamma or X-rays prevented the proliferation of transfused lymphocytes in the recipient by inactivating lymphocytes through cross-linking DNA. They also reported that most cases of TA-GVHD die before diagnosis, and in fact, such reactions may be more prevalent than what is known [5].

Serrano et al., reported that irradiation affected the quality and shelf life of red blood cells by increasing potassium concentration and through hemolysis over time. Therefore, irradiation of every blood product would reduce blood stocks and lead to waste. The optimum is the irradiation of blood products in cases of necessary indications. However, irradiation of platelet suspensions does not affect platelet quality [16].

Jawa et al., associated TA-GVHD with fresh blood components. They stressed that this was probably due to a decline in T-cell viability or antigen expression 2. Morrison et al., recommended the irradiation of erythrocyte suspension at least 14 days after preparation (except for emergencies) [17].

The major limitation of the present study was the irradiation of blood products in different clinics, even though there was no indication for irradiation. While this resulted in no health problems for the patient, it created a problem with regard to cost. Here, we irradiated erythrocyte suspensions and platelet suspensions with gamma rays at doses in accordance with the literature in patients with the indications recommended in the literature. We never encouraged TA-GVHD in any patient for whom we used irradiated blood products.

Conclusion

TA-GVHD is a highly fatal transfusion complication. The most valid method to inhibit the proliferation of lymphocytes that cause TA-GVHD is to irradiate blood and blood products with gamma rays. The blood products can be irradiated for risky patients easily and quickly with the irradiators available in blood centers, and potentially fatal TA-GVHD would be prevented.

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