

Novel Protocol for Rapid Desensitization of Melphalan in a 5-Year-Old Boy Undergoing Conditioning for Hematopoietic Stem Cell Transplantation: A Case Report

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Abstract

Hematopoietic stem cell transplantation is a potentially life-saving therapy under certain conditions. Hypersensitivity reaction to chemotherapeutic drugs may interfere with this treatment. Griscelli syndrome type 2 is a rare autosomal recessive disease characterized by hypopigmentation of skin and hair, causing silver gray hair; this disease may develop a fatal condition called hemophagocytic lymphohistiocytosis. The main curative treatment for hemophagocytic lymphohistiocytosis is hematopoietic stem cell transplantation.

Melphalan is an important drug in hematopoietic stem cell transplantation preparation regimen. This drug is only stable for 60 minutes following reconstitution with normal saline. There is a recommended 12- to 20-step desensitization protocol for moderate to severe hypersensitivity reaction to chemotherapeutic drugs. However, due to the short term stability of melphalan, this protocol cannot be employed in desensitization.

In this case report, we presented a novel protocol for rapid desensitization of melphalan in a 5-year-old boy with immediate, moderate to severe hypersensitivity reaction, during hematopoietic stem cell transplantation.

To obtain 50 mg total melphalan, we prepared solutions of drug in two bags; one with 12.5mg in 35 cc normal saline, and other with 25 mg in 35 cc normal saline. Each solution was infused during 60 minutes by incremental infusion rate, and the total of 50 mg melphalan was successfully infused.

Keywords: Rapid desensitization, Melphalan, Hematopoietic stem cell transplantation, Child

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Introduction

Griscelli syndrome type 2 (GS2) is a rare autosomal recessive disease characterized by hypopigmentation of skin and hair, causing silver gray hair.¹ Due to the abnormal regulation of the immune system, this syndrome leads to a fatal condition called hemophagocytic lymphohistiocytosis (HLH), caused by macrophage hyperactivation. More than 80% of patients with GS2 develop HLH, ensuing death in the absence of allogeneic hematopoietic stem cell transplantation (HSCT).²

We reported a case of 5-year-old boy with classic feature of GS2 and HLH from Mofid children hospital of Tehran, Iran. The case was a candidate for unrelated umbilical cord blood hematopoietic stem cell transplantation. He received reduced intensity conditioning regimen, including fludarabine, melphalan, antithymocyte globulin, and developed an immediate hypersensitivity reaction to high-dose melphalan during conditioning regimen and successful rapid desensitization for immediate hypersensitivity reactions.

Case Presentation

The patient was an only child from related parents, a 5-year-old boy with silver gray hair and no familial history of GS2 and HLH.

At one year old, he had presented with fever, pancytopenia, hepatosplenomegaly, high serum ferritin, and other HLH criteria. In that examination, bone marrow aspiration (BMA) showed erythroid hyperplasia but no hemophagocytosis. EBV and CMV Polymerase chain reaction (PCR) analysis were negative, and more evaluation involving gene analysis was in favor of GS2. Based on HLH diagnosis, the patient received HLH protocol (2004).³

During treatment with HLH protocol, we searched for a related or unrelated full human leukocyte antigen (HLA) matched donor for HSCT as the only definitive treatment. The search for full match donor HLA was not successful, and we had to select an unrelated female cord blood with one missed match for HSCT. The CD34 Cell count of cord blood was $3.6 \times 10^6/\text{kg}$ and viability was 96%. The patient blood group

was A+ and the donor blood group was O+. Following HLH remission, the patient became a candidate for HSCT.

The patient was admitted in our HSCT ward. After the insertion of central venous line (CVL), serum hydration, including 3000 cc Ds + 2meq/100 cc kcl/ intravenous/24 h was commenced on day 9 prior to the infusion of stem cells for HSCT (day -9). For antiemetic prophylaxis, 3 mg ondancetrone was administered 0.5 h before chemotherapy and then every 6 h.

Conditioning regimen was reduced intensity, including fludarabine:30 mg/m² (intravenous /infusion for 5 days, days -8, -7, -6, -5, -4), melphalan:70 mg/m² (intravenous / infusion for 2 days, days -3, -2), and Rabbit antithymocyte globulin(ATG):2.5mg/kg/day(intravenous /infusion for 4 days, days -4,-3, -2, -1).

GVHD prophylaxis was started with cyclosporine at dose 3mg/kg/day, divided q12h, intravenous infusion since day -2 and methylprednisolone at dose 1 mg/kg/day intravenous infusion since day +1.

The patient received fludarabine with no complication on day -8 to day -4. On day -3, five minutes after starting the melphalan infusion (approximately 6 mg), he developed chest pressure, shortness of breath, cough, and severe facial flushing. He had no fever and the blood pressure (BP) was normal. Oxygen saturation was 97% and the evaluation of electrocardiography and chest radiograph was normal. Infusion of melphalan was stopped immediately after the reaction and the symptoms resolved after O₂ therapy by mask, single dose of intravenous diphenhydramine 10 mg, and hydrocortisone 100 mg. Immunology consultation was done, and the patient was immediately visited by the Allergy and Immunology team.

Melphalan was stable for only 60 minutes after reconstitution and had to be diluted in normal saline to a concentration ≤ 0.45 mg/mL. Due to the unique chemical properties of melphalan, we were unable to use the standard 4-bag of drug in a 16-step desensitization protocol.⁴ Accordingly, as shown in table 1, the Allergy and Immunology team designed a novel melphalan desensitization

Table 1. Novel 3-bag 11-step rapid melphalan desensitization protocol

Solution	Dosage (total dose 50 mg/day)	Rate	Time
Solution A	12.5 mg melphalan+35 cc N/S	5 cc/hr	15 min
		10 cc/hr	15 min
		15 cc/hr	15 min
		20 cc/hr	15 min
Solution B	12.5 mg melphalan + 35 cc N/S	20 cc/hr	15 min
		30 cc/hr	15 min
		40 cc/hr	15 min
		50 cc/hr	15 min
Solution C	25 mg melphalan + 70 cc N/S	50 cc/hr	15 min
		60 cc/hr	15 min
		75 cc/hr	To the end of solution

protocol.

The following day, the patient was pre-medicated with 1 mg/kg methylprednisolone, 5 mg/kg cimetidine and 1.25 mg/kg diphenhydramine IV one hour before starting the melphalan. Allergic reaction desensitization drugs, containing epinephrine, diphenhydramine, and methylprednisolone were brought to the bedside. After starting the melphalan, the vital signs were checked every 5 min for 15 min, and then every 10 min. The desensitization procedure was tolerated without any reaction. The following day, the patient received the next 50 mg melphalan dose according to the desensitization protocol; conditioning regimen was continued and he received complete doses of melphalan without anymore problems. Afterwards, conditioning regimen with Rabbit-ATG was continued, and at last, umbilical cord blood transplantation (HSCT) was successfully infused on day 0.

Discussion

The incidence of allergic reactions to intravenous melphalan including anaphylaxis is about 2%.^{4,5} In a study by Cornwell et al., hypersensitivity reactions to intravenous melphalan during treatment of multiple myeloma were observed in 2.4% of the 425 patients receiving intravenous melphalan with or without other drugs, and 3.9% of the 255 patients receiving melphalan alone.⁶

Our patient developed moderate to severe hypersensitivity to melphalan with systemic

reaction in conditioning protocol for HSCT. Based on immunology consultation and their recommended novel 3-bag 11-step rapid desensitization protocol, our patient, just one day later after reaction to melphalan, successfully received and completed the full therapeutic dose of drug.

The tryptase levels were not checked; however, in hypersensitivity reactions, tryptase levels can increase 2- to 5-fold the normal range, indicating systemic mast cell degranulation.⁷ Rapid drug desensitization (RDD) is a modality by which mast cells are rendered hyporesponsive, thereby protecting patients against anaphylaxis.⁸ The mechanism of RDD involves antigenic determinants binding to IgE without cross linking, inhibition of antigen/IgE-bound FcεR1 receptor complex internalization, and downregulation of tyrosine kinases Syk and Lyn.⁹

The Brigham and Women's Desensitization Program generated a flexible 12- to 20-step protocol, delivering $\times 2$ to $\times 2.5$ doses of drug antigens at fixed time intervals starting at 1/1000 to 1/100 dilutions of the final concentration.¹⁰ Protocols with only two bags have been proposed for patients with a mild-to-moderate risk and should be used with extreme caution in highly sensitized patients.¹⁰

Our patient had started conditioning regimen and received fludarabine, in which conditions, it is necessary to receive melphalan. Melphalan has a unique chemical property and is stable only for 60 min; therefore, the 12- to 20-step protocol for desensitization in our patient was not useful. We

designed and successfully used a novel 3-bag 11-step for a rapid desensitization of melphalan.

However, desensitization must be repeated if new courses of the same medication are required.^{8,11}

Conclusion

This new method of desensitization can be applied to medications such as melphalan, which has a short half-life.

Ethical Consideration

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences.

Patient Consent

To publish this case report, written informed consent was obtained from the patients' parents.

Conflict of Interest

None declared.

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