VIA MEDICA

CLINICAL VIGNETTE

Acta Haematologica Polonica 2024
Number 2, Volume 55, pages 123–125
DOI: 10.5603/ahp.98653
ISSN 0001–5814
e-ISSN 2300–7117

Allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia with accompanying hereditary hemorrhagic telangiectasia

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Introduction

Rendu–Osler–Weber disease also known as hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder [1]. It is caused by mutations in the *ENG, ACVRL1* or *SMAD4* genes that result in impaired angiogenesis and vascular remodeling [2].

The Curaçao criteria used for diagnosis include spontaneous recurrent nosebleeds, multiple telangiectasias, visceral lesions including arterio-venous malformations (AVMs) and family history of the disease [3, 4]. Although life-threatening hemorrhages occur only rarely in these patients, the risk of severe bleeding increases with additional coagulopathies and hematological malignancies.

We present an unusual case report of a patient with HHT treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) for high-risk acute lymphoblastic leukemia (ALL).

Case report

In June 2021, a 42-year-old female with *BCR::ABL*p190 positive ALL underwent allo-HSCT in our center. She had been diagnosed with HHT seven years earlier based on the presence of gastrointestinal angiodysplasia, frequent epistaxis, and a positive family history.

Treatment of ALL was according to the Polish Adult Leukemia Group (PALG) ALL7 Ph (+) protocol with rituximab and a tyrosine kinase inhibitor (TKI) i.e. imatinib. Although the first cycle of therapy was well tolerated, complete hematological remission (CHR) was not achieved. As a reinduction therapy, a second generation TKI, dasatinib with dexamethasone was introduced. Seven weeks later, the patient achieved CHR with measurable residual disease (MRD) at 0.36% on flow cytometry (FC) and at 0.06% of *BCR::ABL*p190 IS. She continued dasatinib treatment until the transplantation procedure.

She proceeded to allo-HSCT from a 9/10 HLA-matched unrelated donor (HLA-A mismatch) with minor ABO incompatibility. The source of hematopoietic stem cells was peripheral blood. Total body irradiation of 12 Gy and 6 g of cyclophosphamide were administered as myeloablative conditioning. For graft-versus-host disease (GvHD) prophylaxis, the patient received cyclosporine with methotrexate and anti-thymocyte globulin (thymoglobulin). She developed severe epistaxis, while her conditioned-platelet (PLT) count dropped from 139 G/L on day –3 to 52 G/L on day –2. Antihemorrhagic drugs were administered (i.e. ethamsylate and tranexamic acid) but bleeding recurred on the following days. This required bilateral anterior nasal packing for the next three weeks, plus multiple red blood cells (RBC) as well as platelet (PLT) and plasma transfusions. On day +1 after transplantation, the patient complained of abdominal pain and blood-staine diarrhea. Abdominal computed tomography (CT) excluded gastrointestinal bleeding or tract perforation. In addition, an inflammatory infiltration of the left labia was observed, accompanied by an increase of C-reactive protein up to 159 mg/L (normal range 0–5). Despite the use of broad-spectrum antibiotics, antifungal and antiviral agents, inflammation progressed, leading to the formation of fistula and necrosis that required surgical treatment. *Pseudomonas aeruginosa* was isolated from the lesion,

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Received: 22.12.2023 Accepted: 26.02.2024 Early publication: 01.03.2024

Table I. Disease status before and after allogeneic stem cell transplantation (allo-HSCT) including flow cytometry measurable residual disease (FC-MRD), *BCR::ABL*p190 transcript, and donor chimerism

Time to allo-HSCT	FC-MRD	*BCR::ABL*p190 IS [%]	Donor chimerism [%]
Before transplant	Positive	0.06	–
+ 28 days	Negative	0.025	90
+ 56 days	Negative	0.0025	94
+ 98 days	Negative	0.012	85
Cyclosporine discontinuation			
+ 5 months	Negative	0.073	81
At dasatinib commencement			
+ 6 months	Negative	0.003	100
+ 8.5 months	Negative	0.003	100
After dasatinib discontinuation			
+ 11 months	Negative	Undetectable	100
+ 14 months	Negative	0.004	100
+ 17 months	Negative	0.003	100
+ 20 months	Negative	Undetectable	99
+ 26 months	Negative	Undetectable	100

and targeted antibiotic therapy with colistin was implemented. In total, she received 16 units of RBC and 34 units of PLT transfusions. The patient's overall condition eventually started to improve alongside the normalization of inflammatory markers. She engrafted her neutrocytes and platelets on days +17 and +28 after transplantation, respectively.

Cytomegalovirus reactivation was detected on day +31 and successfully eradicated with valgancyclovir. She was discharged on day +38 after transplantation. Bone marrow biopsy at discharge showed CR with negative MRD-FC and *BCR::ABL*p190 transcript of 0.025% (Table I).

Due to the mixed donor chimerism, the dose of cyclosporin was gradually tapered off. On a follow-up visit two weeks later, she presented acute grade II cutaneous GvHD which was treated effectively with methylprednisolone. A repeated bone marrow biopsy confirmed CR with negative MRD, although donor chimerism had decreased alongside a *BCR::ABL*p190 increase. Dasatinib at a dose of 140 mg daily was initiated, and the treatment resulted in *BCR::ABL*p190 eradication. Dasatinib treatment was eventually stopped nine months after allo-HSCT due to gastrointestinal intolerance (i.e. intense nausea). Currently, 30 months after transplantation, the patient is free of TKIs, with full donor chimerism.

Discussion

In patients with HHT, gastrointestinal bleeding, epistaxis or pulmonary AVMs remain the most common cause of death [5]. Based on the genotype and location of vascular malformations, HHT may be classified as HHT1, HHT2, or juvenile polyposis HHT (JP-HHT). HHT1 is associated with a mutation in the *ENG* gene and poses the highest risk of the development of pulmonary, cerebral and gastrointestinal AVMs. In HHT2, which is caused by a mutation in the *ALK1* gene, hepatic AVMs are common. JP-HHT, with a mutation in the *SMAD4* gene, is characterized by the presence of colorectal hamartomatous polyps [6, 7]. Genetic diagnostics for HHT mutations are not routinely available in Poland. The diagnosis of the disease worldwide is made on the basis of the Curaçao criteria which refer to clinical symptoms.

Myeloablative conditioning rapidly reduces platelet count and impairs gastrointestinal mucosa which can may lead to coagulation disturbances with life-threatening bleeds. Moreover, it is important to remember that dasatinib can cause thrombocytopenia and hemorrhages as a side effect [8]. In a single previous case report, of a 23-year-old patient with Ph(+) ALL and accompanying JP-HHT, despite CR after induction chemotherapy and young age, the patient was not considered for allo-HSCT. Eventually, he relapsed and reinduction therapy with dasatinib was complicated by several episodes of gastrointestinal bleeding, which finally led to his death [9].

Patients suffering from HHT and an aggressive hematological malignancy require special attention. Physicians should be alert to any bleeding symptoms and should not hesitate to perform rapid imaging diagnostics where there is a suspicion of internal bleeding so as to undertake urgent treatment.

Proper management of bleeding can lead to clinical improvements in these high-risk patients, and eventually enable an effective therapy of the underlying hematological malignancy. Despite several life-threatening complications, allo-HSCT was successful in the described patient.

Article information and declarations

Acknowledgments
Not applicable.

Authors contributions
DH, SG — analysis of clinical data, literature search, original draft preparation. AS — supervision, original draft preparation, conceptualization. GH — supervision, writing review and editing.

Conflict of interests
The authors declare no conflict of interests.

Ethics statement
Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

Funding
None.

Supplementary material
None.

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