Clinical Letter

Treatment of graft versus host disease with methotrexate after allogeneic hematopoietic stem cell transplantation

DOI: 10.1111/ddg.14206

Dear Editors,

Graft-versus-host disease (GvHD) is a major complication of allogeneic hematopoietic stem cell transplantation affecting 30–60% of patients despite prophylactic treatment. Acute GvHD (aGvHD) primarily affects the gut, the liver and/or the skin while chronic GvHD (cGvHD) typically resembles rheumatological or autoimmune disorders [1].

The standard for first-line therapy of acute and chronic GvHD are corticosteroids while the second-line treatment is less standardized and includes among others calcineurin inhibitors, mycophenolate mofetil (MMF), mTOR- and JAK2-inhibitors. Methotrexate (MTX) is an established agent for GvHD prophylaxis but not for GvHD treatment [2, 3].

Here, we report the case of a 58-year old female with cutaneous GvHD which was treated by MTX. In April 2013 the patient had a high risk acute myeloid leukemia (AML) and received an HLA-matched allogeneic stem cell transplant from her sister with complete remission in December 2013. Conditioning consisted of a reduced-intensity chemotherapeutic regimen without antithymocyte globulin. Tacrolimus (trough level 5–10 ng/ml) combined with MMF (2 g daily) was used as post-transplant GvHD prophylaxis.

After stopping immunosuppression in June 2014, the patient developed grade II GvHD of the skin, which was treated with systemic steroids until November 2014 in addition to MMF and tacrolimus until June 2015. Since the cutaneous manifestations initially presented as a rash they were classified as aGvHD but reclassified as cGvHD due to subsequent mucosal lesions (September 2015). No photographs or histological specimens were taken during this period. Tacrolimus was tapered until June 2018 summing up to a duration of immunosuppressive therapy of almost five years.

The patient first presented to our dermatology outpatient department in August 2018 with an acute skin rash and oral mucosa lesions for several weeks. Dermatological examination revealed urticarial and partially excoriated papules and plaques in the patient’s face, chest and neck as well as on the back of the hands (Figure 1a, b). In addition, whitish

Figure 1 August 2018: Multiple disseminated urticarial papules and plaques on the patient’s face, accentuated on the cheeks and forehead (a) as well as on the patient’s chest (b). April 2019: After six months of MTX treatment; face, with complete resolution of the lesions on cheeks and forehead (c) and chest (d).
reticulated lesions of the lips and oral mucosa and moderately painful erosions of the cheek mucosa (Figure 2a, b) were noted. The patient reported no other signs or symptoms and general well-being.

A possibly photosensitizing drug taken by the patient was sulfamethoxazole/trimethoprim (960 mg three times per week), started in 2013 as *pneumocystis jirovecii* pneumonia (PjP) prophylaxis after the allogeneic stem cell transplantation.

After admission to our clinic, biopsies of the skin (lower chest) as well as of the oral mucosa were performed. The skin biopsy showed an apoptotic degeneration of basal keratinocytes accompanied by a lympho-histiocytic infiltrate of the upper corium, consistent with an interface dermatitis, which is commonly seen in acute GvHD or various autoimmune diseases such as lupus erythematosus (Figure 3). Laboratory analyses were negative for lupus erythematosus or autoimmune bullous dermatoses (ELISA for Desmoglein 1/3, Ro/La, double-stranded DNA or antinuclear antibodies). The oral mucosa showed a lymphocytic infiltrate of the connective tissue without interface dermatitis. Apart from the skin and oral mucosa, no other organs were affected by GvHD. There was also no microbiological or virological evidence for an infection. Gynecological consultation excluded genital involvement. In summary, the final diagnosis was an overlap GvHD (acute part, grade II).

Systemic therapy with corticosteroids (60 mg prednisolone daily) and MTX (15 mg s.c. once per week) was initiated, with 5 mg folic acid supplementation on the day after MTX application. Further, the cutaneous lesions were locally treated with pimecrolimus. The oral and labial lesions quickly resolved, allowing the tapering of the steroids.

At a follow-up visit in April 2019 (under treatment with MTX 15 mg s.c. weekly and prednisolone 2.5 mg daily) the cutaneous and mucosal lesions were in stable remission (Figures 1c, d and 2c, d).
Interestingly, the patient showed clinical and histological findings consistent with an aGvHD of the skin while the mucosal lesions were suggestive of a cGvHD [2]. According to the National Institutes of Health Consensus Guidelines, acute and chronic GvHD are primarily differentiated based on clinical and diagnostic aspects rather than the time of onset [3, 4]. Therefore, the 100-day rule after bone marrow transplant defining acute versus chronic GvHD is no longer valid [3, 4].

Acute GvHD occurring more than 100 days after allogeneic stem cell transplantation is referred to as “late aGvHD” in the absence of symptoms of cGvHD [3, 4]. The simultaneous presentation of acute and chronic GvHD symptoms - as in our case - is classified as an “overlap chronic GvHD” [3, 4]. However, it is difficult to make a definitive diagnosis solely based on cutaneous/ mucosal manifestations without further organ involvement [3].

Treatment options for GvHD, whether acute or chronic, are limited. Systemic steroids are most commonly used as first-line treatment in both subtypes, often associated with serious side effects due to its long-term use, such as osteoporosis, diabetes and other metabolic complications. Long-term immunosuppression with calcineurin inhibitors, such as cyclosporine and tacrolimus, has been associated with an increased incidence of malignancies [5, 6]. These may be prevented in case of cutaneous GvHD by either phototherapy (especially PUVA or UVA1) or extracorporeal photopheresis [2, 7].

Previous studies of the therapeutic effect of MTX in patients with GvHD are promising. In the study of Inagaki et al., which included 35 pediatric patients with steroid refractory acute GvHD, almost half of the patients showed at least partial remission of the symptoms after only four doses of 10 mg/m² MTX s.c. per week [8]. Neutropenia and thrombocytopenia were observed in 26 % and 49 % of the patients, respectively, with only 9 % developing serious infections [8]. Further, Giaccone et al. showed that MTX allowed reduction of the steroid dose needed to control the symptoms of chronic GvHD in 10/14 patients [9].

In summary, low-dose MTX might be a possible candidate for an effective and safe medium- to long-term therapy of GvHD.

Conflict of interest
None

Benjamin Walz¹, Claus-Philipp Maier¹, Volker Beck², Stephan Forchhammer²

¹) Department of Dermatology, University of Tuebingen, Tuebingen, Germany
²) Department of Internal Medicine II, Hematooncology, University of Tuebingen, Tuebingen, Germany

References
1 Sung AD, Chao NJ. Concise review: acute graft-versus-host disease: immunobiology, prevention, and treatment. Stem Cells Transl Med 2013; 2(1): 25–32.
2 Ziemer M. Graft-versus-host disease of the skin and adjacent mucous membranes. J Dtsch Dermatol Ges 2013; 11(6): 477–95.
3 Schoemans HM, Lee SJ, Ferrara JF et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 2018; 53(11): 1401–15.
4 Filipovich AH, Weisdorf D, Pavletic S et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005; 11(12): 945–56.
5 Marcen R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs 2009; 69(16): 2227–43.
6 Carenco C, Assenat E, Faure S et al. Tacrolimus and the risk of solid cancers after liver transplant: a dose effect relationship. Am J Transplant 2015; 15(3): 678–86.
7 Wagenknecht D, Ziemer M. Successful treatment of sclerotic cutaneous graft-versus-host disease using extracorporeal photopheresis. J Dtsch Dermatol Ges 2020; 18(1): 34–8.
8 Inagaki J, Fukano R, Kodam Y et al. Safety and efficacy of low-dose methotrexate for pediatric patients with steroid-refractory acute graft-versus-host disease after hematopoietic stem cell transplantation. Ann Hematol 2014; 93(4): 645–51.
9 Giaccone L, Martin P, Carpenter P et al. Safety and potential efficacy of low-dose methotrexate for treatment of chronic graft-versus-host disease. Bone Marrow Transplant 2005; 36(4): 337–41.