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Letter to the editor

Fatal acute graft-versus-host disease in Sézary Syndrome treated with Mogamulizumab and hematopoietic cell transplantation

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ABSTRACT

Sézary syndrome (SS) is a rare and aggressive T-cell lymphoma with a poor prognosis in advanced stages. Allogeneic hematopoietic cell transplantation (allo-HCT) offers a potential cure, but complications such as graft-versus-host disease (GvHD) remain a clinical challenge. Mogamulizumab, a humanized anti-CC chemokine receptor 4 (CCR4) antibody, is sometimes used as a bridge to transplantation, but its potential interactions with allo-HCT are unclear. This report describes the case of a 37-year-old man with advanced SS who received mogamulizumab therapy followed by allo-HCT from an HLA-identical sibling donor. The patient developed severe gastrointestinal acute GvHD, which was treated with steroids and infliximab. However, the condition rapidly progressed to severe intestinal symptoms and life-threatening haemorrhagic shock, ultimately resulting in the patient's death. This case highlights a potential link between mogamulizumab and severe acute GvHD promoted by drug-induced suppression of regulatory T cells. Further research is required to fully understand the interaction between mogamulizumab and allo-HCT and to determine whether it is an optimal approach as a bridge to transplant therapy. This paradigmatic case suggests the need of personalizing transplant strategies by selecting appropriate conditioning therapy and GvHD prophylaxis to minimize potential toxicity.

1. Introduction

Sézary Syndrome (SS) is a rare leukemic subtype of cutaneous T-cell lymphoma. The main clinical features include generalized erythroderma, lymphadenopathy and characteristic cerebriform cells circulating in peripheral blood, called Sézary cells. Diagnosis of SS is histopathological, often by skin biopsy, but can be also supported by flow cytometry of peripheral or bone marrow blood, which confirms T-cell origin (CD3+, CD4+) and the lack of mature T-cell antigens (CD2, CD3, CD5, CD7) [1].

Typically, advanced stages of SS have a poor prognosis: in a cohort of 525 patients described by Kim et al. the overall survival rate for cases with T4-stage disease was 41 %, 24 %, and 7 % at 5, 10, and 20 years, respectively [2]. Autologous cell transplantation showed an excellent overall response rate (ORR), but most patients relapsed early after the procedure [3]. Allogeneic hematopoietic cell transplantation (allo-HCT) is preferred due to the combination of high-dose chemotherapy and the graft-versus-lymphoma immunological effect. Studies have confirmed that allo-HCT is the only potentially curative treatment for patients with SS, especially those who have achieved previous disease remission or have a low tumor burden [3].

Mogamulizumab is a humanized anti-CC chemokine receptor 4 (CCR4) antibody that is expressed on different types of cells, including T-regs and helper T-cells, and is overexpressed on malignant T-cells. The mechanism of action is based on enhancing antibody-dependent cellular cytotoxicity, which directly targets malignant T-cells and depletes T-regs that suppress host antitumor immunity. The international phase III randomized trial (MAVORIC) found that mogamulizumab offered an overall response rate of 37 % in relapsed/refractory patients with SS and showed statistically significant superior progression-free survival compared to vorinostat arm. However, the median progression-free survival of 7.7 months was still disappointing [4]. Therefore, mogamolizumab may be a suitable bridging therapy for transplantation.

2. Case presentation

This report presents the case of a 37-year-old man who was diagnosed with SS in 2019. He had previously received treatment with prednisone, interferon-alpha, and extracorporeal photopheresis for two years at another medical center. In 2021, the patient presented at our department with progressing skin disease and a PET/CT scan confirmed stage IVA involvement. Therefore, mogamulizumab therapy was started (1 mg/kg on days 1–8–15–22, followed by days 1–15 from the second cycle, every 28 days) for a total of 21 cycles. This resulted in a partial remission, characterized by the disappearance of generalized erythroderma and no lymph node involvement on CT scans whereas some erythematous plaques persisted. During mogamulizumab therapy, the patient did not experience any major adverse effects. Routine blood tests revealed an elevation in amylase and lipase levels, however no clinical or instrumental signs of pancreatitis were observed. After completing mogamulizumab, the patient underwent six cycles of gemcitabine (1200 mg/m2 on days 1 and 8) as bridging therapy to transplantation to enhance the response achieved.

In January 2023, the patient underwent allo-HCT from a matched, 34-year-old, nulliparous sister. Donor and recipient shared blood type A1Rh+ and had negative CMV status. The conditioning regimen used was the Thiotepa-Busulfan-Fludarabine (TBF) protocol with Cyclosporine A and short-course Methotrexate used for graft versus-host disease (GvHD) prophylaxis. The stem cell source was peripheral blood and the cell dose infused consisted of 4.08 × 10^6 CD34+/kg and 2.3 × 10^8

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CD3+/kg. Engraftment was achieved by day +11 for both granulocytes and platelets.

On day +22, the patient developed a mild and transient cutaneous erythema of the head and upper body (aGvHD grade I: skin +, liver 0, gut 0, according to Glucksberg System Score [5]). From day +27, he started methylprednisolone (2 mg/kg/day) due to aGvHD progression (grade II, skin +++; liver 0; gut 0). By day +33, due to aGvHD worsening, with the appearance of profuse diarrhea and severe abdominal pain (grade IV, skin ++; liver 0, gut ++++), the patient was considered unresponsive to first-line therapy and received infliximab (anti-TNF-α) as a second-line treatment [6]. After the first dose of infliximab (1 mg/Kg), a slight improvement of the abdominal symptoms was observed with gradual resolution of diarrhea and abdominal pain, and a complete skin response.

On day +38, the patient suddenly presented with angina and shortness of breath, which was associated with widespread T-wave inversion on the ECG. This was followed by a life-threatening hemorrhagic shock (severe hematemesis and enterorrhagia), which required admission to the Coronary Care Unit. The patient suffered severe haemorrhage leading to a circulatory arrest and required orotracheal intubation for intensive resuscitation. A CT scan of the chest and abdomen showed distended intestinal loops containing blood and an urgent gastroscopy showed diffuse erosions of the esophago-gastric mucosa. The diagnosis of aGvHD was confirmed through histologic examination of the small intestine (Fig. 1). The patient was receiving low molecular weight heparin treatment for a segmental pulmonary embolism diagnosed on day +36 post-transplant (platels>100 × 109/L). This treatment likely contributed to the bleeding episode.

The patient received three weekly doses of infliximab, but experienced progressive worsening of intestinal aGvHD and died two weeks later.

3. Discussion

SS is an aggressive disease that often requires multiple therapeutic approaches, including allo-HCT, which is the only potentially curative treatment. Although new targeted therapies are available, the interactions and side effects of these drugs in patients undergoing transplantation are not fully understood.

We here reported on a case showing a potential correlation between mogamulizumab and the onset of severe intestinal aGvHD refractory to two lines of therapy.

There are few case series describing the onset of aGvHD after mogamulizumab therapy, suggesting the existence of a potential immune mechanism of action that promotes aGvHD. To date, all case reports about mogamulizumab therapy and aGVHD are from Asian patients who were treated for T-cell acute lymphoblastic leukemia [7,8]. A small report of 8 patients with cutaneous lymphoma treated with mogamulizumab described a grade IV gastrointestinal aGvHD after allo-HCT from an HLA-mismatched donor in one patient [9]. In another report, a patient treated with mogamulizumab developed an aGvHD-like colitis without undergoing allo-HCT. Notably, this patient's intestinal mucosa revealed an inflammatory infiltrate predominantly encompassing naïve T lymphocytes with the absence of Tregs [10].

Some reports suggest that administering mogamulizumab before allo-HCT may increase the risk of aGvHD due to the drug's ability to delete CCR4-expressing regulatory T-regs [9]. This risk appears to be higher if the transplant is performed within 3 months of the last mogamulizumab dose, as T-regs typically return to normal levels 3–4 months after discontinuing the drug [7]. In this patient's case, the last mogamulizumab infusion occurred 5 months before the allo-HCT procedure.

T-regs have several functions in allo-HCT immunology including immune system modulation, promoting graft tolerance, enhancing engraftment and suppressing GvHD. According to the study by Riegel et al. [11], T-reg infusions not only prevent but also effectively treat aGVHD in mouse models. Furthermore, T-regs show significant tropism and immunosuppressive effects in the gastrointestinal tract. Although there are several ongoing clinical trials, the main obstacles to the therapeutic use of T-regs in vivo are their cost and the complexity of manufacturing techniques, which limit their wide reproducibility [12, 13].

To conclude, our case report adds to observations suggesting a possible association between mogamulizumab and aGvHD, despite limited data. Considering the potential risk of mogamulizumab-induced colitis as a rare but documented adverse effect [10], it is crucial to rule out any damage to the intestinal mucosa prior to transplantation. Further research is required to establish the best approach for managing these patients pre- and post-transplantation and the expected benefit from mogamulizumab should be carefully balanced with the substantial risk of serious complications. It may be advantageous to increase the time between the last mogamulizumab administration and allo-HCT to more than 6 months. Alternatively, a reduced-intensity conditioning regimen could be used to reduce intestinal toxicity, especially in case of

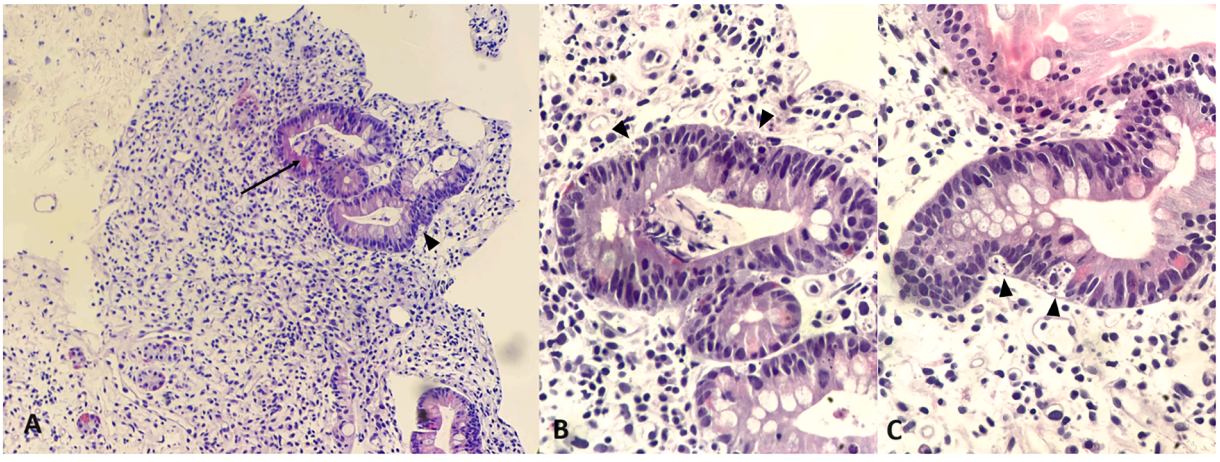

Fig. 1. Histopathological examination of small intestine mucosa at day +38. **A)** Small intestine mucosa with severe chronic inflammation with numerous lymphocytes and plasma cells. Slight fibrosis and crypt architectural changes are observed along with atrophy. This examination also notes the presence of Paneth cells. At this magnification, crypts with some apoptosis are observed on the upper right with initial cleavage of gland epithelium that is suggestive for crypt dropout (arrowhead) (H&E original magnification 4x). **B, C)** At higher magnification, more than 2 apoptosis on contiguous crypts can be readily identified, with the lumen containing cellular debris indicating an initial dropout. These features suggest a grade 2/3 GvHD according to the Lerner system (original magnification 20x, HxE).

pre-existing lesions. Furthermore, monitoring the blood levels of the drug and T-regs count before transplantation can improve the planning and personalization of GvHD prophylaxis and treatment [14]. This is especially important considering the encouraging preliminary results on the clinical application of T-regs [15].

Ethics approval and consent to participate

Review and collection of clinical and molecular data were performed in accordance with the protocols and written consent approved by the institutional review boards of each participating institutions and guidelines set forth by the Declaration of Helsinki.

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Data availability

All data and results of the survey from which results were generated are available in the manuscript. Additional request can be directed via email to the corresponding author.

Consent for publication

Informed consent obtained according to the protocols approved by the Institutional Review Board of the participating institutions and in accordance with the ethical principles set forth by the Declaration of Helsinki.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare no competing financial interests.

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