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Effectiveness of intra-arterial steroid administration for the treatment of steroid-refractory acute gastrointestinal graft-versus-host disease

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ARTICLE INFORMATION

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AIM: To retrospectively assess the clinical effectiveness of intra-arterial steroid administration (IASA) treatment in adult patients who developed steroid-refractory gastrointestinal acute graft-versus-host disease (GI-aGvHD) (≥stage II) following haematopoietic stem cell transplantation.

MATERIALS AND METHODS: Clinical data of 10 consecutive adult patients (age range, 19–61 years; mean age, 42 years) of a single centre with GI-aGvHD (≥stage II) who showed no response to intravenous methylprednisolone and received IASA into the superior (SMA) and/or inferior mesenteric arteries (IMA) were analysed. The severity of aGvHD was determined as the volume of diarrhoea (stages 0–IV) and the Glucksberg grading system before and 12±3 SD, 27±4 and 54±6 days after IASA treatment. Median follow-up was 65 days (range, 22–370 days).

RESULTS: Six out of 10 patients at 12 days, 8/10 patients at 27 days, 6/10 patients at 54 days after IASA showed gastrointestinal response. Among them, 1/10 patients at 12 days, 4/10 patients at 27 days, and the same 4/10 patients at 54 days showed complete resolution of GI-aGvHD. The 4/10 patients who reached complete resolution of GI-aGvHD at day 12 or 27 showed a sustained symptom-free state. One in 10 patient showed only a temporary response, 5/10 patients died between days 22 and 67.

CONCLUSIONS: IASA seems to be a potentially useful second-line therapy for intravenous steroid-refractory GI-aGvHD.

Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is a commonly used treatment for haematological malignancies. Acute graft-versus-host disease (aGvHD) is a potentially fatal complication of allogeneic HSCT and occurs

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in 40–50% of cases.[1,2] The main cause of aGvHD is the difference between the major/minor histocompatibility antigenic profile between the donor and recipient cells, which leads to organ dysfunction, particularly in the skin, liver, and gastrointestinal (GI) tract through cellular (cytotoxic T cells) and inflammatory effectors (tumour necrosis factor [TNF]-α, interleukin [IL]-1).[3–6]

aGvHD most commonly affects the skin, resulting in maculopapular rash.[7] Hepatic GvHD manifests in elevated serum alkaline phosphatase and bilirubin levels.[8] aGvHD of the GI tract presents with voluminous, sometimes bloody diarrhoea, nausea, vomiting, abdominal pain, and ileus.[9]

The prognosis of aGvHD is poor with a survival rate below 5% for grade IV disease; however, in grade I the survival rate is >90%.[10] First-line treatment of aGvHD are systemic corticosteroids, which results in sustained improvement in less than half of the patients.[11] Patients who are refractory to steroid treatment have a mortality rate exceeding 90%.[12]

Intra-arterial steroid administration (IASA) into the superior (SMA) and/or inferior mesenteric arteries (IMA) is a second-line treatment for GI-aGvHD described by a limited number of publications.[13–15] The aim of the present study was to evaluate the therapeutic efficacy of IASA treatment in adult patients with steroid-refractory GI-aGvHD (≥stage II).

Materials and methods

The present study was performed according to the World Medical Association Declaration of Helsinki. All patients gave written informed consent both to the procedure and also to the collection of their clinical data for research purposes; IRB approval was given (44703-4/2018/EKU).

The study population consisted of 10 adult patients (mean age: 42 years, range: 19–61 years) with haematological malignancy who had allogeneic HSCT and subsequently developed GI-aGvHD (≥stage II) and failed to respond to intravenous methylprednisolone (≥2 mg/kg/day). All patients were treated with IASA between March 2015 and January 2016. Clinical data of patients were collected to retrospectively evaluate the therapeutic efficacy of IASA treatment. The clinical characteristics of the patients are shown in Table 1.

IASA procedure

Catheter-guided angiography of the mesenteric arteries was carried out under local anaesthesia. Femoral/brachial arterial access with 4 F catheters was applied, followed by injection of 1 mg/kg methylprednisolone into the SMA and IMA using end-hole-only catheters. The injection lasted for 5 minutes each time. In case of a platelet count <50 G/L, the Angio-Seal Vascular Closure Device was used to safely achieve haemostasis.

Severity of GvHD

The stage of GI-aGvHD was determined according to the volume of diarrhoea (Table 2)[16] before and 12±3 [SD], 27±4

Table 1
Clinical characteristics of patients treated with intra-arterial steroid administration (IASA).

Patient no.	Age (years)	Sex	Diagnosis	HLA match	Conditioning regimen	GvHD prophylaxis	Time between allo-HSCT–aGvHD (days)	aGvHD therapy (before IASA)	Time between aGvHD–IASA (days)	aGvHD therapy (after IASA)
1	44	M	MF	12/12	Bu/Flu/ATG	Tacrolimus, methotrexate	113	Steroid, tacrolimus	26	Steroid, alemtuzumab
2	19	F	MDS	11/12	Bu/Flu/ATG	Sirolimus, tacrolimus	41	Steroid, MMF, sirolimus, rituximab, ECP	253	Steroid, MMF, sirolimus, budesonide, tacrolimus, ECP
3	41	F	AML	12/12	Bu/Flu	Cyclosporin A, methotrexate	64	Steroid, alemtuzumab, rituximab, ruxolitinib	304	Steroid, calcineurin inhibitor, budesonide, ruxolitinib
4	41	M	AML	10/12	Bu/Flu/ATG	Sirolimus, tacrolimus	54	Steroid, tacrolimus	49	Steroid, tacrolimus
5	55	M	MDS	11/12	Treo/Bu/ATG	Cyclosporin A, methotrexate	38	Steroid, ruxolitinib, alemtuzumab	46	Steroid, tacrolimus, sirolimus
6	23	M	Pre-B-ALL	12/12	TBI/Cy	Sirolimus, tacrolimus	34	Steroid, tacrolimus, budesonide	29	Steroid, tacrolimus, budesonide
7	38	F	AML	7/8	Bu/Flu/Cy/ATG	Sirolimus, MMF	23	Steroid, tacrolimus	75	Steroid, sirolimus, alemtuzumab
8	61	M	MDS	12/12	Bu/Flu	Cyclosporin A, MMF	33	Steroid, sirolimus	91	Steroid, MMF, ATG
9	55	M	Pre-T-ALL	12/12	Bu/Flu/ATG	Sirolimus, tacrolimus	94	Steroid, MMF	45	Steroid, MMF, budesonide
10	47	M	Pre-B-ALL	11/12	TBI/VP16	Alemtuzumab, tacrolimus, sirolimus	17	Steroid, tacrolimus, MMF, rituximab	159	Steroid, calcineurin inhibitor, budesonide, MSC

MF, myelofibrosis; MDS, myelodisplastic syndrome; AML, acute myeloid leukaemia; Pre-B-ALL, precursor B-cell acute lymphoblastic leukaemia/lymphoma; Pre-T-ALL, precursor T-cell acute lymphoblastic leukaemia/lymphoma; Bu, busulfan; Treo, treosulfan; Flu, fludarabine; ATG, anti T-cell globulin; TBI, total body irradiation; Cy, cyclophosphamide; VP16, etoposide; MMF, mycophenolate mofetil; ECP, extracorporeal photopheresis; MSC, mesenchymal stromal cells.

Table 2
Gastrointestinal acute graft-versus-host disease (GI-aGvHD) stages determined by the volume of diarrhoea[16].

GI-aGvHD stage	Diarrhoea
0	No
I	500–1,000 ml/day
II	1,000–1,500 ml/day
III	>1,500 ml/day
IV	>1,500 ml/day; abdominal pain or ileus

Table 3
Gastrointestinal acute graft-versus-host disease (GI-aGvHD) grades determined by the gastrointestinal involvement and the Eastern Cooperative Oncology Group (ECOG) performance status[18].

	GI-aGvHD grade
I	No gut involvement; no decrease in clinical performance
II	Stage I gut involvement; mild decrease in clinical performance
III	Stage II or III gut involvement; marked decrease in clinical performance
IV	Stage II–IV gut involvement; extreme decrease in clinical performance

and 54±6 days after IASA. The Glucksberg classification system[17,18] was used to assess overall GvHD grade at the same time points (Table 3).

Results

The results are summarised in Tables 4 and 5. In nine patients, 1×1 mg/kg methylprednisolone was given into the SMA and IMA. In one patient, the IMA showed poor filling, therefore this patient received 2x1 mg/kg methylprednisolone only into the SMA. There were no complications during the intra-arterial procedures.

Four of 10 patients had stage II, 2/10 patients had stage III, and 4/10 patients had stage IV GI-aGvHD; 7/10 patients had grade IV and 3/10 patients had grade III aGvHD prior to IASA treatment. Twelve days after IASA, 6/10 patients at 27 days, 8/10 patients at 54 days, 6/10 patients showed some degree (partial or complete) of gastrointestinal response. Among them, 1/10 patients at 12 days, 4/10 patients at 27 days and the same four patients at 54 days showed complete resolution of GI-aGVHD (i.e., stage 0). The 4/10 patients who reached complete resolution of GI-GvHD at day 12 or 27 showed a sustained symptom-free state. One of the 10 patients showed only temporary response. Five of the 10 patients died between days 22 and 67, and the percentage of fatal outcome was the same in stages II, III, and IV (Fig 1).

Discussion

Three recent studies on 11–19 patients suggested that IASA has a significant therapeutic benefit in patients who received HSCT and subsequently developed steroid-resistant aGvHD.[13–15] There are different ways to assess therapeutic response after IASA. Weintraub *et al.*[15] defined the date of patient discharge as the time of determining therapeutic response. They classified patient response as periprocedural death or partial or complete response. Partial response indicates patient discharge on total parenteral nutrition (TPN) and oral medications, whereas complete response indicates patient discharge on oral nutrition and oral medications. Out of 11 patients involved in the study, three patients (27%) died periprocedurally from GvHD- or heart-related complications. Four patients (36%) showed partial response and four patients (36%) achieved complete remission at discharge. At a mean follow-up time of 566 days (range, 542–614 days), three patients (27%) were alive.[15]

Nishimoto *et al.*[14] evaluated the GI response at 28 days after the first IASA treatment and used the categories of complete response, partial response, and no response. The IASA-treated group of 19 patients achieved a complete response with a significantly higher rate than the control group of 14 patients (63% versus 21%, $p=0.033$) At 180 days, the overall survival rate was higher in the IASA-treated group compared to the control group (79% versus 50%, $p=0.109$).[14]

Bürgler *et al.*[13] assessed the changes in aGvHD grade and GI-aGvHD stage 28 days after IASA treatment. Out of the 12 patients enrolled, 10 patients (83%) showed gastrointestinal response and four patients (33%) reached complete

Table 4
Gastrointestinal acute graft-versus-host disease (GI-aGvHD) stages before and 12±3 [SD], 27±4 and 54±6 days after intra-arterial steroid administration (IASA) with follow-up results.

Patient number	GI-aGvHD stage before IASA	GI-aGvHD stage 12 days after IASA	GI-aGvHD stage 27 days after IASA	GI-aGvHD stage 54 days after IASA	Follow-up results and duration (days)
1	Stage IV	Stage IV	Stage III	–	Deceased (52)
2	Stage III	Stage I	Stage 0	Stage 0	Stage 0 (370)
3	Stage II	Stage II	Stage II	Stage II	Deceased (61)
4	Stage II	Stage I	Stage 0	Stage 0	Stage 0 (297)
5	Stage IV	Stage IV	Stage II	Stage I	Deceased (67)
6	Stage II	Stage I	Stage 0	Stage 0	Stage 0 (195)
7	Stage III	Stage II	Stage II	–	Deceased (27)
8	Stage II	Stage II	–	–	Deceased (22)
9	Stage IV	Stage 0	Stage 0	Stage 0	Stage 0 (87)
10	Stage IV	Stage I	Stage III	Stage III	Stage IV (63)
Partial response	–	5/10	4/10	2/10	0/10
Complete response (stage 0)		1/10	4/10	4/10	4/10

Table 5
Gastrointestinal acute graft-versus-host disease (aGvHD) grades prior to and 12±3 [SD], 27±4 and 54±6 days after intra-arterial steroid administration (IASA).

Patient number	aGvHD grade before IASA	aGvHD grade 12 days after IASA	aGvHD grade 27 days after IASA	aGvHD grade 54 days after IASA
1	Grade IV	Grade IV	Grade IV	Deceased (day 52)
2	Grade IV	Grade II	≤ Grade I	≤ Grade I
3	Grade IV	Grade IV	Grade IV	Grade IV
4	Grade III	≤ Grade I	≤ Grade I	≤ Grade I
5	Grade IV	Grade IV	Grade III	Grade II
6	Grade IV	Grade II	≤ Grade I	≤ Grade I
7	Grade III	Grade IV	Grade IV	Deceased (day 27)
8	Grade III	Grade III	–	Deceased (day 22)
9	Grade IV	≤ Grade I	≤ Grade I	≤ Grade I
10	Grade IV	Grade II	Grade III	Grade III

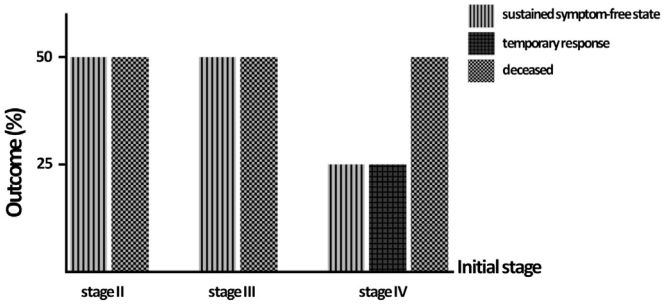

Figure 1 Treatment outcomes according to baseline stage groups.

response at day 28. Five patients (42%) were alive at a median follow-up time of 531 days.[13]

The results of the present study are consistent with the findings of Bürgler *et al.*,[13] as 80% of patients showed gastrointestinal improvement at 27 days including 40% of patients who achieved a complete response.

The high rate of favourable outcomes after IASA may be explained by the advantages of local steroid treatment over systemic dosing as the inflamed intestinal tissue has a lower number of steroid receptors with a decreased affinity. Furthermore, increasing the doses of systemic steroids would result in greater mortality, mainly due to infectious complications. Thus, localised steroid injection may result in a greater therapeutic response.[19,20] The intra-arterial procedures showed no complications in the present study; it has also been shown to be safe in other publications.[13–15]

The limitations of the current study are the relatively small number of patients, the retrospective manner of investigation, and the clinical heterogeneity of the patients, including differences in pharmacological treatment.

In summary, IASA is a safe and effective method to treat steroid-refractory GI-aGvHD in patients who have failed to respond to first-line treatment with intravenous steroids. Further investigations are needed to obtain a more accurate assessment of the effectiveness of IASA and to reveal the possible prognostic factors associated with a successful outcome.

Conflict of interest

The authors declare no conflict of interest.

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