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Stem Cell Transplantation

Feasibility of early tapering of cyclosporine following reduced-intensity stem cell transplantation for advanced hematologic or solid malignancies

Although some researchers have reported that early tapering of cyclosporine is feasible and beneficial to augment graft-versus-leukemia effects after conventional stem-cell transplantation, there is little information on the feasibility of this strategy following reduced-intensity stem cell transplantation (RIST). We summarized outcomes of 17 patients who underwent early tapering of cyclosporine following RIST from HLA-identical siblings.

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There are some reports that early tapering of cyclosporine is feasible and beneficial to augment a graft-versus-leukemia (GVL) effect after conventional allogeneic stem cell transplantation (allo-SCT),[1,2] while there is little information on the feasibility of this procedure following reduced-intensity stem cell transplantation (RIST). We summarized the outcomes of 17 patients with a median age of 53 years (range, 25-61) who underwent early tapering of cyclosporine following RIST from HLA-identical siblings from 1999 to 2003 in our hospital. Nine had chemorefractory hematologic malignancies and eight had advanced solid tumors. Preparative regimens comprised fludarabine/busulfan (n=16),[3] and cladribine/busulfan (n=1).[4] Eight patients with solid tumors received rabbit antithymocyte globulin (ATG) 2.5 mg/kg for 4 or 2 days.[4] Graft-versus-host disease (GVHD) prophylaxis was continuous infusion of cyclosporine 3 mg/kg/day. Early tapering of cyclosporine was defined as completion of tapering by day 60. We intended to continue tapering even if the patients developed GVHD during this dose reduction. If GVHD was tolerable the patients received

Table 1. Clinical features of acute and chronic GVHD.

Case	Tapering period (days)	Acute GVHD (maximum stages and grade)	Onset of acute GVHD (Day after transplant)	Treatment of acute GVHD	Interval between the onset of GVHD and initiation of its treatment (days)	Duration of corticosteroid use*1(days)	Outcome of acute GVHD	Chronic GVHD	Type of chronic GVHD	Onset of chronic GVHD (day after transplant)	Treatment of chronic GVHD	Outcome of chronic GVHD
Preparative regimens without ATG												
1	25-35*2	skin 3 liver 0 gut 0 (II)	35	mPSL 1 mg/kg	2	9	CR					
		skin 2 liver 0 gut 1 (II)	54	mPSL 1 mg/kg	1	9	CR	NE				
2	29-55*2	skin 3 liver 0 gut 0 (II)	47	cyclosporine			CR	yes	de novo extensive	113	mPSL 1 mg/kg	NC
3	22-36	skin 1 liver 2 gut 1 (II)	57	mPSL 2 mg/kg, ATG, MMF	0	51	MR	no				
4	22-25	no GVHD						NE				
10	30-41	skin 3 liver 0 gut 2 (III)	41	mPSL 0.5 mg/kg	0	7	CR	yes	quiescent extensive	121	none	PD
12	19-25*2	skin 0 liver 0 gut 3 (III)	23	mPSL 2 mg/kg	3	39	PR	yes	quiescent extensive	327	mPSL 1 mg/kg	PR
		skin 0 liver 0 gut 3 (III)	82	mPSL 2 mg/kg	0	42	CR					
13	30-45	skin 0 liver 3 gut 0 (III)	71	PSL 1 mg/kg	15	14	CR	yes	quiescent extensive	148	PSL 1 mg/kg	PR
15	30-45	skin 1 liver 0 gut 2 (III)	63	PSL 1 mg/kg	9	15	PR	yes	progressive extensive	NE	PSL 1 mg/kg	PR
17	30-45	skin 2 liver 2 gut 3 (III)	58	PSL 1 mg/kg	15	8	PR	no				
Preparative regimens with ATG												
5	20-44	skin 2 liver 0 gut 3 (III)	21	none			CR	yes	progressive limited	NE	none	CR
6	43-45	skin 3 liver 0 gut 3 (III)	54	cyclosporine			CR	yes	quiescent extensive*3	150	none	CR
7	30-45	no GVHD						yes	*de novo* extensive*4	129	none	CR
8	32-46	no GVHD						no				
9	27-57	no GVHD						no				
11	31-44	no GVHD						no				
14	30-45	no GVHD						no				
16	30-45	no GVHD						yes	*de novo* extensive	117	none	NC

*mPSL: methylprednisolone; PSL: prednisolone; MMF: mycophenolate mofetil, CR, complete response; PR: partial response; NC: no change; MR: mixed response; NE: not evaluable. *1Use of more than 0.5 mg/kg methylprednisolone. (Doses of prednisolone were converted into those of methylprednisolone). *2Tapering of cyclosporine was discontinued because of the development of acute GVHD (Cases 1, 2, and 12). *3Case 6 developed GVHD after administration of interferon-α. *4Case 7 developed liver GVHD and autoimmune hepatitis after administration of interferon-α.*

Table 2. Effect of ATG on GVHD, transplant-related mortality and infections.

Preparative regimens	*With ATG (n=8)*	*Without ATG (n=9)*
Acute GVHD, grade II to IV	2	8
Chronic GVHD	4	5*
Transplant-related mortality	0	4
Documented infections associated with GVHD	0	2
Cytomegalovirus antigenemia	8	9

*GVHD: graft-versus-host disease; ATG: antithymocyte globulin. *7 evaluable patients.*

supportive therapy at the discretion of the primary physicians. If GVHD was intolerable, we first increased cyclosporine and then, if the patient's conditions did not improve, methylprednisolone was added at a dose of 1-2 mg/kg/day.

All the patients achieved sustained engraftment. None developed grade III to IV regimen-related toxicity according to the Seattle criteria.[5] Tapering of cyclosporine was not completed in three patients who developed GVHD. Early tapering was suspended and they continued to receive cyclosporine. GVHD improved with cyclosporine alone in one patient, whereas corticosteroids were needed in the other two patients. Ten patients developed grade II-IV acute GVHD (Table 1), with a maximum grade of II (n=3) and III (n=7). The median onset of GVHD was day 51 (range, 21-71). Acute GVHD resolved without corticosteroids in three patients. The remaining seven were given corticosteroids. The initial response to corticosteroids was complete remission (CR) in three, partial response (PR) in three, and mixed response in one. After the initial response, GVHD recurred or progressed in two. These two patients were treated again with corticosteroid, and both achieved CR. Of the four patients who did not achieve CR after the initial treatment, three died of GVHD and/or complicated infections. The other patient achieved durable CR after the repeated administration of corticosteroids. Nine of the 15 patients who survived longer than 100 days developed chronic GVHD; progressive (n=2), quiescent (n=4), and *de novo* (n=3). The other manifestations included brochiolitis obliterans with organizing pneumonia and corneal perforation associated with keratoconjunctivitis sicca,[6] persistent diarrhea, chronic renal failure due to renal tubular damage,[7] and autoimmune hepatitis. There was a significant difference in the incidence of grade II-IV acute GVHD between patients who received ATG and those who did not (p=0.0152) (Table 2). The incidences of chronic GVHD, transplant-related mortality (TRM) and documented infections tended to be low in patients given ATG.

The median follow-up of the surviving patients was 14.4 months (range, 12.0-25.3). Transplant-related mortality (TRM) within 100 days and 1 year was 6% (1/17) and 24% (4/17), respectively. Its causes included acute GVHD (n=2), chronic GVHD (n=1), and fulminant hepatitis due to reactivation of hepatitis B virus (n=1). Seven patients with hematologic malignancies obtained CR. Six of the 7 patients had developed acute and/or chronic GVHD. Four patients achieved durable CR lasting longer than 6 months. No patients with solid tumors obtained a complete or partial response regardless of the presence of GVHD.

This study demonstrates that the feasibility of early tapering of cyclosporine is associated with the types of preparative regimens. Of the eight patients given ATG-containing regimens, none died of transplant-related causes. The incidence of acute GVHD was comparable to that previously reported for allogeneic stem cell transplants, in which cyclosporine was usually tapered.[8,9] In contrast, high incidences of GVHD, TRM and infectious episodes were noted in RIST without ATG. Rapid tapering of cyclosporine is not acceptable in its present form. However, it should be noted that four of the eight patients who developed grade II to IV acute GVHD following RIST without ATG achieved remission lasting longer than 180 days. Because it is impossible to eliminate or control refractory hematologic malignancies by reducecd-intensity preparative regimens alone, it is reasonable to speculate that early tapering of cyclosporine following RIST without ATG has a powerful anti-leukemia activity.

While this small-sized retrospective study has several limitations, it does suggest that early tapering of cyclosporine might be beneficial to induce a GVL effect following RIST. However, the feasibility of this strategy depends on the use of ATG, and GVHD is not acceptable in RIST without ATG. We should investigate other ways of intervening after RIST in patients with high-risk hematologic malignancies.

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Key words: early cyclosporine withdrawal, reduced intensity stem cell transplantation, antithymocyte globulin.

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Stem Cell Transplantation

New insights into the pathophysiology of gastrointestinal graft-versus-host disease using capsule endoscopy

We investigated gastrointestinal graft-versus-host-disease using capsule endoscopy in patients with abdominal pain and/or diarrhea. We found severe pathology involving most of the gut including loss of villi, ulcerations, narrowing, bleeding and fistula formation. In 2 patients, capsule endoscopy alone established the diagnosis of graft-versus-host-disease. Some ulcerations were associated with cytomegalovirus infection.

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Fourteen patients with gastrointestinal graft-versus-host disease (GVHD)) acute (n=11), or signs of chronic GVHD with diarrhea, abdominal pain or malabsorption (n=3) were studied by using capsule endoscopy. GVHD was graded according to the International Bone Marrow Transplant Registry (IBMTR) indices.[1] Routine stool examinations were done. The median grade of acute gastrointestinal-GVHD was C (range B-D). Two of the patients had reactivation of cytomegalovirus (CMV) diagnosed by pp65 antigenemia, while one had borderline results. Capsule endoscopy is the only minimally invasive method for direct visualization of the entire small intestine. The system uses a disposable miniature video camera contained in a capsule, which is ingested by the patient. The capsule passes through the digestive tract, transmitting high quality color images during 6-7 hours. Capsule endoscopy has been proven to be effective in the diagnosis of diseases of the small bowel such as tumors and inflammatory bowel disease and in identifying the source of gastrointestinal bleeding.[2,3] In this study we used a GIVEN M2A capsule (Yoqneam, Israel) which was ingested after a 12-hour fast and 30 minutes after administration of metoclopramide. Patients were followed for abdominal symptoms with attention to the stool to identify the capsule. No symptoms of obstruction were recorded and all the capsules were retrieved. One patient died 7 days after capsule endoscopy due to sepsis. There

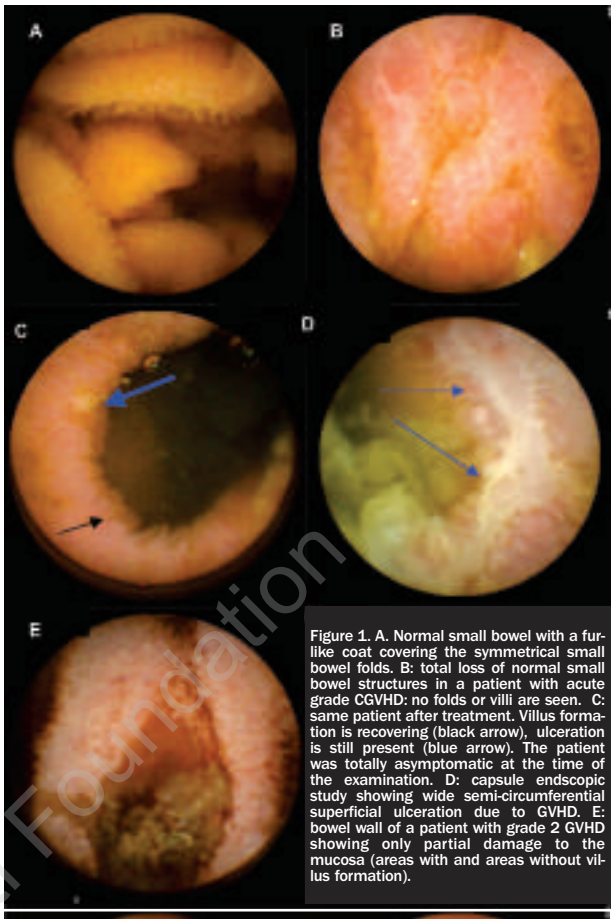

Figure 1. A. Normal small bowel with a fur-like coat covering the symmetrical small bowel folds. B: total loss of normal small bowel structures in a patient with acute grade CGVHD: no folds or villi are seen. C: same patient after treatment. Villus formation is recovering (black arrow), ulceration is still present (blue arrow). The patient was totally asymptomatic at the time of the examination. D: capsule endscopic study showing wide semi-circumferential superficial ulceration due to GVHD. E: bowel wall of a patient with grade 2 GVHD showing only partial damage to the mucosa (areas with and areas without villus formation).

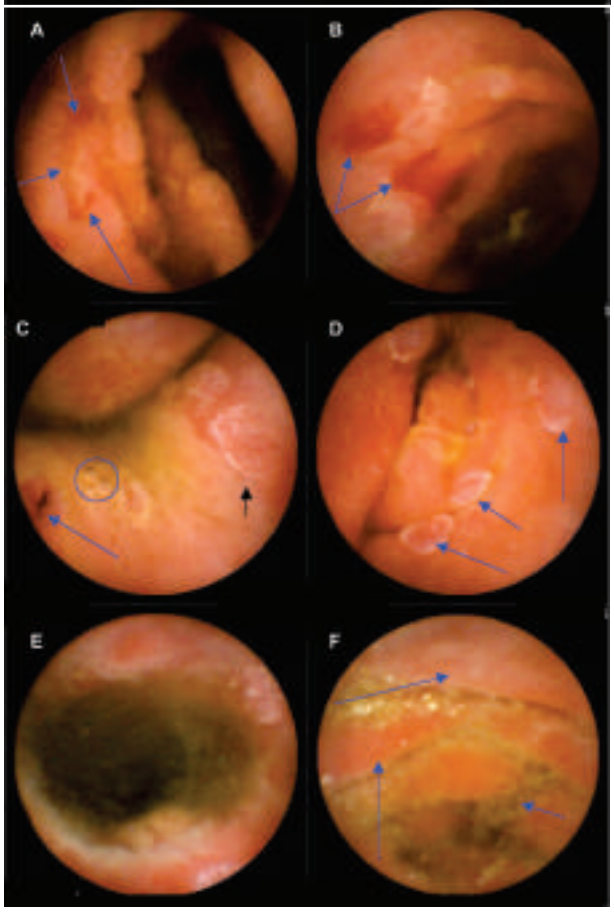

Figure 2 [right column, low panel]. A: small bowel with deep ulceration between the blue arrows, most probably due to CMV infection; this patient had positive pp65 CMV antigenemia. B: small bowel wall lacking villi with spontaneous bleeding (blue arrows). C: intestinal mucosal covered with multiple diffuse aphthous lesions (blue arrows) in a patient with grade 4 GVHD; no villi can be seen. D: same patient as in picture 2C with aphthous lesions (short black arrow). The orifice of an entero-enteric fistula can be seen (long blue arrow); note the air bubbles (circled), which exit via the fistula. E: circumferential luminal narrowing in a patient with grade 4 GVHD; note the absence of villi and peripheral aphthous lesions. F: irregular thickened folds, with mucoid discharge adherent to surface of the mucosa in a patient with grade 4 GVHD. Typically, villi are absent.