Alemtuzumab for Severe Steroid-Refractory Gastrointestinal Acute Graft-versus-Host Disease

Mathieu Meunier [1,*], Claude Eric Bulabois [1], Anne Thiebaut-Bertrand [1], Raphaël Itzykson [2], Martin Carre [1], Sylvain Carras [1], Fréderic Garban [1,3], Jean Yves Cahn [1]

[1] Clinique d'hématologie, CHU de Grenoble, UMR 5525 CNRS-UJF, France
[2] Service d'hématologie-greffe, Hôpital Saint-Louis, Assistance Publique, hôpitaux de Paris, Université Paris, France
[3] Etablissement français du sang, CHU de Grenoble, UMR 5525 CNRS-UJF, France

Article history:
Received 26 March 2014
Accepted 28 May 2014

Key Words:
Allogeneic hematopoietic cell transplantation
Acute graft-versus-host disease
Antibody therapy
Alemtuzumab

A B S T R A C T

Acute graft-versus-host disease (aGVHD) still remains the main cause of morbidity and mortality after allogeneic stem cell transplantation. Moreover, patients who did not respond to first-line treatment with glucocorticosteroids have a very poor outcome. Some studies suggested that alemtuzumab (a humanized monoclonal antibody against the CD52 antigen) might be effective for treatment of refractory aGVHD. Here we report a single-center experience with alemtuzumab in refractory gastrointestinal aGVHD. From September 2009 to April 2012 at the Grenoble medical university center, 24 patients who had presented a refractory gastrointestinal aGVHD to corticosteroid, or after another immunosuppressive drug, were retrospectively analyzed. Most patients (n = 19) presented stage 4 gastrointestinal aGVHD. Response to treatment (either complete or partial) was observed in 15 patients (62.4%). The overall survival rate at 1 year for all patients was 33.3% (95% confidence interval [CI], 15.9% to 51.9%) and for responders, 53.3% (95% CI, 26.3% to 74.4%). Two patients died from infection, 5 patients from recurrent GVHD, and 1 from an uncontrolled post-transplant lymphoproliferative disorder.

INTRODUCTION

Bone marrow transplant is a widespread procedure for treatment of hematologic malignancies like acute leukemia. Worldwide, about 50,000 allogeneic hematopoietic stem cell transplantations are performed each year [1]. Although some progress has been made in acute graft-versus-host disease (aGVHD) prophylaxis, its occurrence remains common, with prevalence from 35% to 45% in recipients of fully matched sibling donor grafts to 60% to 80% in recipients of 1-antigen HLA-mismatched unrelated donor grafts [2,3]. aGVHD is still the major cause of morbidity and mortality after stem cell transplantation. Initial treatment usually includes high-dose glucocorticosteroids, with a response rate of 30% to 70% [4-6]. The prognosis for patients who do not respond remains poor [7]. Although a consensus exists for the first-line treatment of aGVHD, there is no consensus as to second-line treatment, and the choice of the second immunosuppressive agent depends on the experience of the clinical team [8]. Several second-line treatments have been tried in the past, such as antithymoglobulin, tacrolimus, mycophenolate mofetil, antitumor necrosis factor, and anti-interleukin 2 receptor, with response rates of around 30% to 50% [9-14].

Alemtuzumab (a humanized monoclonal antibody against the CD52 antigen) is an immunosuppressive drug targeting the CD52 antigen expressed on T cells, B lymphocytes, monocytes, dendritic cells, macrophages, and eosinophils. All these immune cells can be involved in GVHD [15]. Alemtuzumab is also used for the prevention of GVHD [16,17], and some studies have already shown the efficiency of alemtuzumab in steroid-refractory GVHD [18,19]. Here, we investigated the effectiveness of alemtuzumab for refractory gastrointestinal aGVHD in 24 patients.

METHODS

Patients

We identified all patients who had developed a gastrointestinal steroid-refractory aGVHD or a gastrointestinal aGVHD resistant to another line of immunosuppressive drug after corticosteroids and were treated by alemtuzumab at Grenoble University Hospital (France) between September 1, 2009 and April 1, 2012. The diagnosis of gastrointestinal aGVHD was based on clinical criteria according to National Institutes of Health guidelines [20] and was confirmed both endoscopically and histologically for most patients. Steroid-refractory aGVHD was defined by worsening under 2 mg/kg/day of prednisolone over at least 4 days or by no improvements in grades III to IV aGVHD after at least 14 days of prednisone therapy (2 mg/kg/day). Gastrointestinal GVHD was considered as being acute if acute and profuse diarrhea and abdominal pain were clinically confirmed, independently of the time interval after hematopoietic stem cell transplantation [21].

Treatment Schedule

All patients signed a written consent for data collection and analysis concerning all the complications linked to the graft procedure. After giving oral approval, patients received a first dose of 30 mg alemtuzumab intravenously. Patients who did not show any improvement of aGVHD symptoms in the first 2 weeks after the injection were given 2 subsequent injections (with a 2-week interval between each injection).

To improve the tolerance of alemtuzumab, all patients were premedicated by injection of 1 g paracetamol and 1 mg/kg methylprednisolone. Methylprednisolone used for the first-line therapy was slowly tapered off after alemtuzumab injection, and other immunosuppressive drugs were stopped.

Evaluation of Response, Toxicities, and Infections

Response was evaluated clinically by daily staging and grading of aGVHD from the first day of alemtuzumab treatment onward. Complete response was defined as the full resolution of rectal bleeding, abdominal pain, and diarrhea without the use of an antimotility agent and/or antalgics. Persistent aGVHD was diagnosed when clinical symptoms remained unchanged or worsened. We considered the response to be partial when there was a

Financial disclosure: See Acknowledgment on page 1454.

* Correspondence and reprint request: Mathieu Meunier, Clinique d'hématologie, CHU de Grenoble, UMR 5525 CNRS-UJF, France.
E-mail address: mmeunier2@chu-grenoble.fr (M. Meunier).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.05.031

Table 1
Patients Characteristic

Patient Identification Number	Gender	Age at Transplant (yr)	Disease	Donor Type	Mismatch	Graft Source	aGVHD Grade	Stage of GI aGVHD	Stage of Liver aGVHD	Treatment Before Alemtuzumab (Including Steroids)	Overall GVHD Response	OS (d)	Viral Complication	Cause of Death
391075	F	60	AML	MMD	A-allele	PBSCs	4	4	2	anti-TNF	CR	251	EBV reactivation	GVH with multiorgan failure
98059861	M	43	AML	MMD	C-allele	PBSCs	4	4	0	anti-TNF	NR	78		GVH with multiorgan failure
412050	F	41	AML	MUD		PBSCs	4	4	3	tacro+evrl, anti-TNF, EPC	NR	2	CMV reactivation	GVH with multiorgan failure
93023633	M	55	ML	MUD		PBSCs	4	4	0	tacro+evrl, anti-TNF	CR	516		Pneumopathy with severe hypoxemia
424542	F	22	MDS	SIB		PBSCs	4	4	0	tacro+evrl, anti-TNF	NR	18		GVH with multiorgan failure
609479	M	23	ALL	MUD		PBSCs	4	4	0	tacro+evrl, anti-TNF	NR	11	EBV reactivation	GVH with multiorgan failure
390519	M	56	FL	SIB		PBSCs	4	4	1	tacro+evrl, anti-TNF	NR	27		GVH with multiorgan failure
362942	F	51	MM	MUD		BM	4	4	0	tacro+evrl, anti-TNF, MTX	CR	1076		Alive
605704	F	52	AML	SIB		PBSCs	3	3	0	tacro+evrl	CR	1233	CMV reactivation	Alive
97038870	M	55	CLL	MUD		PBSCs	4	4	0	Evrl	CR	235		GVH with multiorgan failure+ infection
618602	M	41	ALL	SIB		BM	3	2	0	Evrl	CR	1006	EBV reactivation	Alive
360934	M	58	MDS	MUD		PBSCs	4	4	0	Evrl	CR	971		Alive
641362	F	53	AML	MUD		PBSCs	4	4	0		NR	189	CMV reactivation	GVH with multiorgan failure
643027	M	48	AML	MMD	C-allele	PBSCs	4	4	2		NR	6	EBV reactivation	GVH with multiorgan failure
385311	M	62	ML	SIB		PBSCs	4	4	0		NR	39	EBV reactivation	GVH with multiorgan failure
169506	M	59	ML	MUD		PBSCs	4	4	0		CR	637	CMV reactivation	Alive
684128	M	60	AML	MUD		PBSCs	4	4	0		CR	310	CMV reactivation	uncontrolled PTLD
95050077	M	46	CLL	MUD		PBSCs	4	4	0		PR	477	CMV reactivation	Alive
163593	M	62	MM	MUD		PBSCs	4	4	3	tacro	PR	95		Sepsis choc
364740	M	63	MDS	MUD		PBSCs	3	3	0		PR	155	CMV reactivation	GVH with multiorgan failure
167502	M	52	AML	SIB		PBSCs	3	3	1		CR	447		Alive
307119	M	48	MM	MUD		PBSCs	4	4	0		NR	78	CMV reactivation	GVH with multiorgan failure
686434	M	59	AML	MMD	A-allele	PBSCs	3	3	0		CR	129	CMV reactivation PTLD	GVH with multiorgan failure
98041938	F	67	ATL	MUD		PBSCs	4	4	0		PR	69		GVH with multiorgan failure

GI indicates gastrointestinal; AML, acute myeloid leukemia; MMD, mismatched donor; PBSCs, peripheral blood stem cells; CR, complete response; NR, nonresponse; MUD, matched unrelated donor; tacro, tacrolimus; evrl, everolimus; EPC, extracorporeal photopheresis; ML, marginal lymphoma; MDS, myelodysplastic syndrome; MTX, methotrexate; SIB, sibling donor; ALL, acute lymphoblatsic leukemia; FL, follicular lymphoma; BM, bone marrow; MM, multiple myeloma; PR, partial response; CLL, chronic lymphocytic leukemia; PTLD, post-transplant lymphoproliferative disorder; ATL, angioimmunoblastic T cell lymphoma.