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LETTER TO THE EDITOR

Lack of efficacy of rituximab in refractory sclerodermatous chronic GVHD

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Advances in the understanding of cGVHD have implicated B lymphocytes in its pathophysiology.[1] A number of studies have explored the use of the antiCD20 MoAb rituximab in the treatment of patients with steroid-refractory cGVHD. These studies yielded varying findings regarding organ-specific responses. Data on cutaneous cGVHD are available from two prospective studies and four retrospective studies involving a total of 67 patients so far. In a recent review and meta-analysis, Mohamed *et al.*[1] reported that responses were impressive in cases of sclerodermatous or lichenoid cutaneous cGVHD. We detail our experience with the use of rituximab in sclerodermatous GVHD, which is different from that reported previously.

We retrospectively reviewed the medical records of patients with steroid-refractory cutaneous cGVHD treated with rituximab. Patients were treated with rituximab 375 mg/m^2 weekly for three to four doses. Determination of response was based on the records of the clinician and whether additional immunosuppressive agents were added after rituximab therapy for non-response or progression of disease. We followed the response criteria given by Zaja *et al.*:[2] CR in case of complete resolution of cGVHD manifestations; PR in cases of 50% or more regression of cGVHD manifestations; no response (NR) less than 50% improvement, or exacerbation during or after therapy.

Nine patients received rituximab for cGVHD. All were males with a median age of 53 (34–61) years (Table 1). Eight patients had extensive cGVHD with sclerodermatous involvement of skin and s.c. tissues, and one had erythroderma. All patients had at least one other organ involved along with the cutaneous GVHD. Four patients had two or more organs affected (Table 1). The median time from transplantation to the diagnosis of chronic GVHD was 14 months (range 6–60 months). The median time from chronic GVHD diagnosis to rituximab administration was 16 months (range 2–61), and the median time from transplantation to rituximab administration was 33 months (range 13–81). The first line of treatment was prednisolone in all patients. Subsequent treatments included a variety of immunosuppressive drugs such as CYA, tacrolimus, mycophenolate, sirolimus, etanercept, acitretin, UV B radiation, extracorporeal photopheresis and romidepsin, or combinations of those, generally combined with prednisolone. Patients had received these drugs for a median of 17 months (range 3–55 months) before starting rituximab. Rituximab was used at the conventional dose of 375 mg/m^2 weekly. It was the third line of treatment for two patients and the fourth line or more in seven cases. Five patients received three and four patients received four i.v. infusions. The median follow-up after rituximab was 19 months (range 1–27 months). During rituximab administration, patients continued on baseline immunosuppressive therapy. None of our patients achieved a complete or partial response. Although there was an initial temporary improvement in two patients during the first couple of months, both patients failed to sustain their response. Six months after initiation of rituximab, there was no improvement in four patients, and progression of disease with extension of sclerosis in two patients. At the end of one year, among the six alive, sclerosis had progressed in three, remained stable in two patients, with one patient showing slight improvement with softening of skin in one area. Four patients were treated with additional immunosuppressive agents such as acitretin, imatinib and MTX following the administration of rituximab.

A prospective study in Japan,[3] observed histological improvement in three patients with sclerodermatous cGVHD who had responses occurring between 60 and 90 days from initiation of therapy. Maximum follow-up in this study was only 4 months, and the patients who showed improvement had only ocular and oral involvement together with the skin. Cutler *et al.*[4] reported a decrease in median body surface area involved with sclerodermatous GVHD from 35 to 25% after two cycles of therapy, followed by a further decrease to 20% at 1 year after the initiation of rituximab. The outcome in our patients has been disappointing. This may be related to the use of the medication in a different population cohort. Our patients had a severe form of the disease and were started on rituximab as a third or more line of treatment, and compared with the other studies mentioned, the median transplantation-rituximab interval in our cohort was higher (23/33 months), although the interval between the onset of GVHD and rituximab was comparable (13.8/16 months).[4] All had at least one other internal organ involved together with extensive sclerodermatous skin involvement and other comorbidities. It could also be possible that more than one cycle of rituximab (consisting of 4 weekly doses) should be used. In some cases, up to three courses of rituximab were used to elicit some response.[4] Finally, although the efficacy of rituximab in cGVHD is thought to be due to depletion of CD20+ B cells, other mechanisms not involving B cells might also be dominant in sustaining the dysregulated immune response in cGVHD leading to the cutaneous and systemic manifestations.[5] Further clinical studies are needed to evaluate more precisely the outcome of rituximab in steroid refractory sclerodermatous cGVHD.

Table 1 Clinical data and treatment outcomes

Age/sex/Dx/type of donor	*Prior Rx*	*TGI (months)*	*TRI (months)*	*%BSA involved*	*Other organs*	*Outcome*	*After 6 months*	*After 1 year*
60/M/NHL/MSD	P, MMF, T, S	20	81	36	Gut	NR	Extension on abdomen	Softer on abdomen
61/M/AML/MUD	P, CYA, T	9	44	63	Liver	NR	Stable sclerosis	Died of H1N109 infection 8 months
40/M/CML/MSD	P, CYA	7	14	45	Liver	NR	Died of sepsis after 3 months	
53/M/AML/MUD	P, E	11	13	99	Liver	NR	Died within a month due to relapse	
44/M/ALL/MSD	P, MMF, T, CYA, ECP	24	78	63	Eyes, lungs and joints	NR	Added acitretin	Progressed
51/M/CML/MSD	S, T, UVB, R	60	76	63	Liver, lung, muscles and nerves	NR	Stable sclerosis	Stable sclerosis
55/M MDS/MSD	P, T, CYA	19	33	72	Colon	NR	Marginal improvement	Started imatinib
34/M/NHL/MSD	P, T, MMF	14	28	99	Lungs and eyes	NR	No improvement	Added acitretin
55/M/CLL/MSD	P, T, S, A	6	25	90	Gut and liver	NR	No improvement	Still sclerotic

Abbreviations: A = acitretin; BSA = body surface area; Dx = diagnosis; E = etarnecept; ECP = extracorporeal photopheresis; M = Male; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MSD = matched sibling donor; MUD = matched unrelated donor; NHL = non Hodgkin's lymphoma; P = prednisolone; Rx = treament; S = sirolimus; TRI = transplant-rituximab interval; TGI = transplant-GVHD interval; T = tacrolimus.

Conflict of interest

The authors declare no conflict of interest.

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