CASE REPORT

Drugs 2006; 66 Suppl. 2: 29–31
0012-6667/06/0002-0029/$44.95/0

Conversion from Mycophenolate Mofetil to Enteric-coated Mycophenolate Sodium (*myfortic*®) in a Patient with Graft-versus-host Disease

Frédérique Kuhnowski, Louis Terriou, Leonardo Magro, Jean-Pierre Jouet and *Ibrahim Yakoub-Agha*

Service des Maladies du Sang, UAM allogreffes de CSH, CHRU, Lille, France

1. Case Study

The patient was 58 years old in September 2002 when he was diagnosed with chronic myeloid leukaemia (CML). He was first treated using IFN-α, to which aracytine was soon added. By February 2003, hyperleukocytosis with myelocytosis was still present so the interferon was replaced by imatinib. The patient's condition continued to deteriorate, and the haematopoietic cell count started to increase in August 2003.

In September 2003, the patient underwent allogeneic haematopoietic stem cell transplantation with peripheral stem cells from a human leukocyte antigen-matched brother after a busulfan-based non-myeloablative conditioning regimen. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine 3 mg/kg per day and short-course methotrexate. Subsequent changes in the immunosuppressive regimen are summarised in table I. On day 15 posttransplant, a differential count clearly indicated recrudescence of the CML, with a total white blood cell count of $65\,000 \times 10^9$/l, including 70% myeloid cells. In response to this, cyclosporine was discontinued because there was no evidence of GVHD, and treatment with imatinib (400 mg/day) and low-dose busulfan (2 mg/day by mouth) was started. A complete cytogenetic and molecular remission was observed unexpectedly within 2 months.

On day 19, grade II cutaneous GVHD developed, with no gastrointestinal symptoms. The patient was given methylprednisolone followed by anti-IL-2 antibody therapy (Leucotac®) for 4 days. The symptoms failed to improve by day 46, however, and treatment with mycophenolate mofetil (MMF) was started at a dose of 1000 mg twice a day. The patient quickly developed severe diarrhoea two to three times a day responsible for a body weight loss of 5% within one week, and 18 days after the introduction of MMF (i.e. on day 64) it was withdrawn and replaced with enteric-coated mycophenolate sodium (EC-MPS; *myfortic*®) at a dose of 720 mg twice a day. The gastrointestinal symptoms quickly resolved after conversion from MMF to EC-MPS and the GVHD steadily waned.

In January 2004, 4 months posttransplantation, the GVHD flared up again so the corticosteroid dose was increased to 80 mg/day, and tacrolimus 2 mg twice a day was started. In the face of persistent GVHD, this regimen of EC-MPS 720 mg twice a day, prednisolone 80 mg/day and tacrolimus 2 mg twice a day was maintained until March 2004 when the patient developed acute kidney failure and tacrolimus was discontinued. As the GVHD appeared to be under control, the corticosteroid dose was tapered downwards, starting in May 2004. The patient is still alive in good condition and in complete molecular remission from his CML.

Table I. Time course of immunosuppressant drugs after allogeneic haematopoietic stem cell transplantation

Time	Drug	Dose	Reason for change
Transplant	Cyclosporine	3 mg/kg/day	
	Short-course methotrexate	15 ml/m^2/day day 1 10 ml/m^2/day day 3 and 6	
Day 15	Imatinib	400 mg/day	Recrudescence of the CML
	Busulfan	2 mg/day per os	
Day 19	Methylprednisolone	160 mg/day	Grade II cutaneous GVHD
	Leucotac®		
Day 23	Methylprednisolone	160 mg/day	
Day 46	Mycophenolate mofetil	1000 mg b.i.d.	No improvement in symptoms
	Methylprednisolone	160 mg/day with gradual decrease to 80 mg/day	
Day 64	EC-MPS	720 mg b.i.d.	Severe diarrhoea
	Methylprednisolone	80 mg/day	
Month 4	EC-MPS	720 mg b.i.d.	Persistent GVHD
	Prednisolone	80 mg/day	
	Tacrolimus	2 mg b.i.d.	
Month 6	EC-MPS	720 mg b.i.d.	Acute kidney failure
	Tacrolimus	2 mg b.i.d.	
Month 8	EC-MPS	720 mg b.i.d.	Control of GVHD
	Tacrolimus	2 mg b.i.d.	

b.i.d. = Twice a day; **CML** = chronic myeloid leukaemia; **EC-MPS** = enteric-coated mycophenolate sodium; **GVHD** = graft-versus-host disease.

2. Discussion

In this patient, conversion from MMF to EC-MPS resulted in the disappearance of gastrointestinal symptoms, and the GVHD also regressed.

Transplantation of allogeneic haematopoietic stem cells is associated with both acute and chronic GVHD,[1] and prophylaxis and treatment of GVHD is paramount if mortality and morbidity are to be kept to a minimum. The use of immunosuppressive regimens based on a variety of different drugs (notably cyclosporine) has reduced the incidence and severity of GVHD, but in some refractory cases the addition of MMF can lead to remission. The early work of Basara et al.[2] showed that a combination of MMF with cyclosporine and prednisolone led to an improvement in 71% of cases of acute GVHD and in 50% of cases of chronic GVHD. Since then, a number of studies have confirmed the beneficial effects of MMF, not only in the treatment of GVHD,[3,4] but also in its prevention.[5] However, MMF is associated with a relatively high incidence of gastrointestinal problems (27–40%).[3,4] As MMF and EC-MPS are different formulations of mycophenolic acid, there may be a beneficial role for EC-MPS: MMF is a prodrug that is converted into the active moiety in the stomach, whereas EC-MPS is an enteric-coated formulation that was designed to improve gastrointestinal safety. The case reported here suggests that mycophenolate sodium is effective in treating GVHD, and could be used instead of MMF to avoid adverse gastrointestinal reactions, although larger scale studies are warranted to confirm this observation.

References

1. Baron F, Storb R, Little MT. Hematopoietic cell transplantation: five decades of progress. Arch Med Res 2003; 34: 528-44
2. Basara N, Blau WI, Kiehl MG, et al. Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. Transplant Proc 1998; 30: 4087-9
3. Busca A, Saroglia EM, Lanino E, et al. Mycophenolate mofetil (MMF) as therapy for refractory chronic GVHD (cGVHD) in children receiving bone marrow transplantation. Bone Marrow Transplant 2000; 25: 1067-71
4. Kim JG, Sohn SK, Kim DH, et al. Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. Eur J Haematol 2004; 73: 56-61

5. Bolwell B, Sobecks R, Pohlman B, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. Bone Marrow Transplant 2004; 34: 621-5

Correspondence and offprints: *I. Yakoub-Agha*, MD, Service des Maladies du Sang, UAM Allogreffes de CSH, CHRU, Lille, France.
Tel: +33 3 20 44 55 51; fax: +33 3 20 44 94 40;
e-mail: i-yakoub-agha@chru-lille.fr