

## LETTER TO THE EDITOR

# Long-term graft-versus-Waldenström macroglobulinemia effect following reduced intensity conditioning allogeneic stem cell transplantation

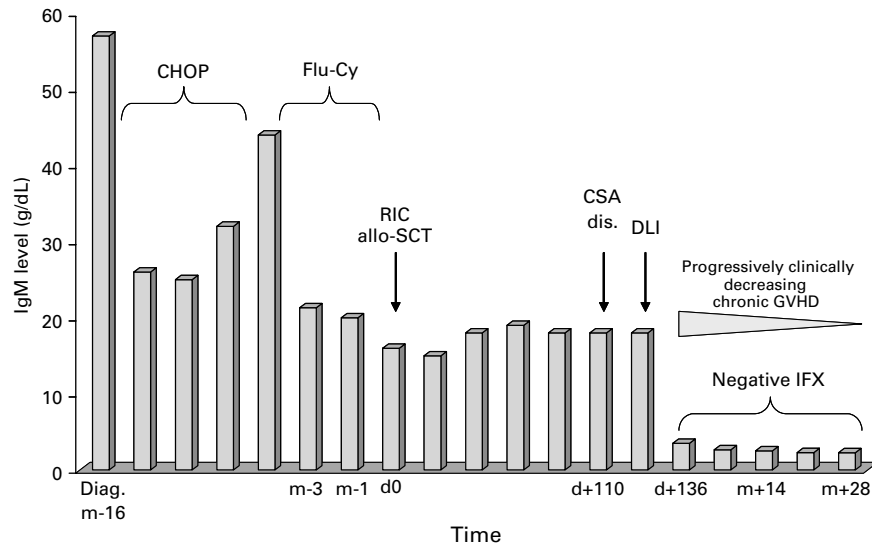
*Bone Marrow Transplantation* (2007) **40**, 175–177;  
doi:10.1038/sj.bmt.1705702; published online 14 May 2007

Waldenström's macroglobulinemia (WM) is a rare B cell lymphoproliferative disorder of the elderly. In symptomatic WM, recent guidelines recommend the use of rituximab and nucleoside analogues (fludarabine) with or without alkylating agents as front-line treatment.<sup>1</sup> However, such therapies can only achieve complete remission (CR) rates ranging from 10 to 40%.<sup>2</sup> The use of high-dose chemotherapy and autologous stem cell transplantation (SCT) may lead to interesting results.<sup>3–5</sup> However, most patients will ultimately relapse, highlighting the need for novel therapeutic approaches, especially in younger patients or those with very aggressive disease. We report here the long-term follow-up of a WM patient successfully treated with reduced intensity conditioning (RIC) allogeneic SCT (allo-SCT).

In May 2003, a 52-year-old male with a previous history of type II diabetes was diagnosed with a WM after a routine blood test. On physical examination, he did not present with any significant clinical symptoms. White blood cell count showed  $4.2 \times 10^9/l$  with 47% lymphocytes, a platelet count of  $104 \times 10^9/l$  and a hemoglobin level of 12.2 g/dl. The IgM monoclonal component was measured at 55 g/dl. Bone marrow aspirate showed 86% of lymphoplasmacytic cells compatible with WM. Computed tomography scan did not show any major organ involvement, but several abdominal and mediastinal small lymph nodes (1–2 cm) were visualized. The patient was clinically asymptomatic, but because of the very high level of monoclonal component, the patient was treated with six courses of CHOP chemotherapy. This treatment had little efficacy on the level of the IgM monoclonal component or bone marrow infiltration. Another six courses of a second-line chemotherapy including fludarabine and cyclophosphamide were performed. The patient achieved only 70% reduction of the IgM monoclonal component. Therefore, the patient was judged as having an aggressive disease, and RIC allo-SCT from his HLA-matched sister was performed. The preparative regimen included fludarabine  $150 \text{ mg/m}^2$ , busulfan  $8 \text{ mg/kg}$  and  $2.5 \text{ mg/kg}$  antithymocyte globulin (thymoglobulin; Genzyme) and a G-CSF-mobilized peripheral blood stem cell graft. Cyclosporine A (CSA) alone was used for GVHD prophylaxis. No grade 3–4 toxicities were observed during conditioning. ANC  $>0.5 \times 10^9/l$  and platelets  $>20 \times 10^9/l$  were achieved by day 21 and 14 after allo-SCT, respectively. The patient did not develop signs of acute GVHD and CSA was discontinued at day 115 after allo-SCT. Two weeks after

CSA discontinuation, the patient was still in mixed T cell chimerism in the peripheral blood (87% of cells of donor origin), had no GVHD signs and still had a high IgM level at 18 g/dl. Therefore, he received a donor lymphocyte infusion (DLI) of  $1 \times 10^6 \text{ CD3}^+/\text{kg}$ . After DLI, the patient converted to full donor chimerism and developed extensive chronic GVHD (skin, mucosa and liver) that required systemic immunosuppressive therapy before being controlled. With a follow-up of 28 months after allo-SCT, the patient is still alive in CR (negative immunofixation at several controls), with signs of moderate limited chronic GVHD, but with a very good performance status (Karnofsky score, 100%) allowing him to resume his job as soccer coach for young children. Figure 1 depicts the concomitant evolution of the IgM level and GVHD after RIC allo-SCT.

WM is probably an incurable lymphoid malignancy with a median survival of 87 months.<sup>6</sup> Allo-SCT is not a classical indication for WM and only few cases have been reported thus far (Table 1). However, an immune graft-versus-tumor (GVT) effect was already suggested after conventional allo-SCT. Although it remains difficult in the standard allo-SCT setting to determine the relative contribution of the myeloablative conditioning and the allogeneic effect, GVT effect was suggested since responding patients experienced simultaneous chronic GVHD and were still in CR several years after allo-SCT.<sup>3,7,8</sup> Unfortunately, among 13 myeloablative allo-SCT cases reviewed here, six (46%) died of early transplant-related mortality (TRM). Since the median age at diagnosis of WM is around 67 years and because of this high risk of TRM, a RIC regimen is probably a more valid option. Among the previously published cases of RIC allo-SCT for WM, and due to short follow-up, a genuine GVT effect and long-term sustained CR could not be documented. The current case has a relatively long-term follow-up of more than 2 years. Moreover, a potent GVT effect was induced with relatively little toxicity, since allo-SCT was performed with evidence of high disease burden (IgM = 16 g/dl), and CR was achieved concomitantly to GVHD onset. Obviously, one could discuss the role of fludarabine contained within the RIC regimen in disease response. However, such hypothesis is likely to be untrue because the patient was previously only partially responder to a second-line fludarabine-based chemotherapy. In all, this case suggests that RIC allo-SCT is a potentially curative option for WM refractory to standard chemotherapy. Given the relatively low incidence of TRM associated with the use of nonmyeloablative and less toxic preparative regimens and based on the recently proposed 'lymphoma like' prognostic index for WM,<sup>6,9</sup> we conclude that if an HLA-matched sibling is identified,



**Figure 1** Relationship between GVHD and monoclonal component (IgM) decrease. This pattern provides evidence for a graft-versus-WM effect. Abbreviations: Diag. = diagnosis; Flu-Cy = fludarabine and cyclophosphamide; CSA dis. = cyclosporine A discontinuation; DLI = donor lymphocyte infusion; IFX = immunofixation; d = day; m = month.

**Table 1** Reported cases of patients with WM who underwent allo-SCT

Reference	Study type	Patients	GVT (suggested)	Survival	Relapse	TRM
Ueda <i>et al.</i> <sup>7</sup>	Case report	n = 1 (RIC)	Yes (cGVHD)	CR at 5 months	No	No
Martino <i>et al.</i> <sup>8</sup>	Case report	n = 2 (MA)	Yes (cGVHD)	PR at 9 years and CR at 3 years	No	No
Tournilhac <i>et al.</i> <sup>3</sup>	Retrospective study	n = 10 MA = 9 RIC = 1 (all heavily pre-treated)	Yes (DLI efficacy)	60% (3–76 months FU) all in CR	No	40% (all were in progression)
Anagnostopoulos <i>et al.</i> <sup>5</sup>	Retrospective study	n = 3 chemo-resistant (MA = 2; RIC = 1)	NA	No CR achieved; two MA = death at 1 month and 6 months of GVHD; one RIC died at 24 months	NA	2/2 (MA)
Dreger (3rd International Workshop on WM, Paris 2004)	Case reports	n = 4 (RIC) heavily pretreated	Yes post-DLI with cGVHD	Three CR achieved	NA	No
Anagnostopoulos <i>et al.</i> <sup>4</sup>	Retrospective study	n = 26 50% chemo-resistant MA = 21 RIC = 5	NA (high progression rate)	46% at 3 years (NA data for the RIC subgroup)	70% at 3 years (NA data for the RIC subgroup)	40% (NA data for the RIC subgroup)

Abbreviations: allo-SCT = allogeneic stem cell transplantation; cGVHD = chronic GVHD; CR = complete remission; DLI = donor lymphocyte infusion; FU = follow-up; GVT = graft-versus-tumor; MA = myeloablative conditioning; NA = not available; PR = partial remission; RIC = reduced intensity conditioning; TRM = tumor-related mortality.

RIC allo-SCT should be considered even in elderly or heavily pretreated patients.

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