Sustained complete remission with single agent rituximab in relapsed follicular lymphoma as transformed disease after unrelated reduced intensity conditioning allogeneic stem cell transplantation

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To cite this version:
Noemí Puig, María D. Caballero, Miguel Alcoceba, Elena Sebastián, Ana Balanzategui, et al.. Sustained complete remission with single agent rituximab in relapsed follicular lymphoma as transformed disease after unrelated reduced intensity conditioning allogeneic stem cell transplantation. Annals of Hematology, Springer Verlag, 2010, 90 (2), pp.227-229. 10.1007/s00277-010-0987-0. hal-00554989

HAL Id: hal-00554989
https://hal.archives-ouvertes.fr/hal-00554989
Submitted on 12 Jan 2011

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Title: Sustained Complete Remission with Single Agent Rituximab in Relapsed Follicular Lymphoma as Transformed Disease after Unrelated Reduced Intensity Conditioning Allogeneic Stem Cell Transplantation

Article Type: Letter to the Editor

Keywords: Transformed DLBCL; RIC-allogeneic stem cell transplantation; rituximab; graft versus lymphoma

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Abstract: According to the instructions, no abstract is needed in Letters to the Editor.
Sustained Complete Remission with Single Agent Rituximab in Relapsed
Follicular Lymphoma as Transformed Disease after Unrelated Reduced Intensity
Conditioning Allogeneic Stem Cell Transplantation

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Word count: 478
A 42 year-old female presented with a right submandibular mass and was diagnosed with stage IVA grade II follicular lymphoma. After receiving multiple lines of treatment, (including CHOP, FMD, autologous transplant, rituximab and yttrium-90-ibritumomab) she underwent an unrelated, HLA-mismatched (9/10), non-myeloablative, allogeneic peripheral blood stem cell transplantation in partial remission December 29th, 2006. Conditioning regimen consisted of fludarabine and melphalan [1]. Cyclosporin and mycophenolate-mofetil were used as graft-versus host disease (GVHD) prophylaxis. Patient and donor had EBV IgG antibodies. Complete chimerism was documented on day +28, remaining stable up to date. She developed grade II (skin III, gastrointestinal I) acute GVHD managed with metil-prednisolone (2mg/Kg) and beclometasone (2mg/6h). Signs and symptoms subsided on day +54 and steroids were tapered.

On day +100, she presented with a right inguinal mass. PET/CT-scan showed right iliac (1.5x2.5cm) and inguinal (3x1.5cm) lymphadenopaties, the latter FDG avid (SUV10.5). Incisional biopsy of the right inguinal node showed DLBCL with a proliferation index of 90%; EBV was negative; qualitative PCR showed the presence of the BCL2/JH (Mbr) rearrangement; cytogenetics and FISH detected the t(14;18) with no other added lesions; GeneScanning analysis and sequencing of the immunoglobulin chain gene rearrangement V\_k-Kde was identical to that detected at diagnosis confirming the re-appearance of the malignant clone and thus the diagnosis of relapsed disease transformed to diffuse large B cell lymphoma (Fig.1a) [2]. Flow cytometric analysis on lymphadenopathy cell suspensions identified a B-cell malignancy intermingled with a polyclonal T-cell population representing 42% of the cellularity; chimerism analysis (STR&GeneScanning) detected 42% of donor cells and 58% of patient cells (fig.1b). Taken together, results can be explained by the presence in the sample of patient-derived clonal B-cells together with infiltrating T-cell lymphocytes (TIL-T) of donor origin, findings suggestive of an active graft versus lymphoma effect.
Baseline immunosuppression was reduced and she received 4 doses of single agent rituximab at a standard dose. Three months later, re-evaluation with PET/CT and bone marrow biopsy showed complete remission. She developed chronic GVHD affecting the gastrointestinal tract and joints (+874) and is currently taking tacrolimus and steroids at a low-dose. Repeated follow-up imaging, including the most recent PET/CT scan (February09) showed no significant abnormalities. There is no evidence of disease in the last bone marrow assessment (March09).

In summary, our patient presented with a rapidly enlarging, PET positive, right inguinal node early post-allotransplant. A post-transplant lymphoproliferative disorder was suspected but an identical immunoglobulin chain gene rearrangement to that detected at diagnosis was identified, confirming the diagnosis of relapsed lymphoma transformed to DLBCL. The frequency of this entity is unknown since most studies do not specify/confirm histologies at relapse [3-6]. Despite the poor prognosis of transformed follicular lymphoma [7], our patient remains clinically and radiologically in complete remission on day +915 post-transplant. It is likely rituximab and a GVL effect exerted by a TIL-T population and forced by reducing the immunosuppression influenced the outcome of our patient [8,9].

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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FIGURE LEGENDS

Figure 1a. GeneScanning analysis of kappa light chain immunoglobulin rearrangement (V<sub>K</sub>-Kde) at diagnosis and at relapse post-allogeneic stem cell transplantation. Note that PCR product size is similar in both samples and therefore highly suggestive of relapsed disease.

Figure 1b. Chimerism analysis at relapse post-allogeneic transplantation showing recipient, donor and recipient´s adenopathy short tandem repeat (STR) genotypes. Focused on shadowed peaks in adenopathy sample, arrows point out peaks of recipient origin.
Figure 1a

**DIAGNOSIS**

- RECEPIENT SAMPLE
- DONOR SAMPLE
- RELAPSE POST-TRANSPLANT SAMPLE

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Figure 1b

**a) RECEPIENT SAMPLE**

**b) DONOR SAMPLE**

**c) RELAPSE POST-TRANSPLANT SAMPLE**
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