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Case report

Successful HLA haploidentical myeloablative stem cell transplantation for aggressive hepatosplenic alpha/beta (αβ) T-cell lymphoma

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ABSTRACT

Hepatosplenic T cell lymphoma (HSTCL) is a type of hematologic neoplasia with a poor prognosis and a high frequency of refractoriness to conventional chemotherapy. The results obtained by high dose chemotherapy followed by autologous stem cells transplantation seem to be a more effective option but still unsatisfactory. Also the role of allogeneic stem cell transplantation is still unclear, although the few cases reported on the literature would seem to show good results in overall survival rates.

In this paper, we reported the patient's medical history affected by a αβ variant of hepatosplenic T cell successfully rescued with a haploidentical transplant.

1. Introduction

Hepatosplenic T cell lymphoma (HSTCL) is a very rare type of hematologic malignancy, making up about 5% of peripheral T-cell lymphomas. It predominantly affects young male adults, with a higher incidence in patients submitted to immunosuppressive treatment for chronic inflammatory bowel disease. This unfrequent lymphoma is characterized by extranodal infiltration of mature malignant post-thymic T-lymphocytes into sinusoids of the liver and spleen, so it usually presents with hepatosplenomegaly (without lymphadenopathy) and the presence of peripheral blood cytopenia, which reflects a high incidence of bone marrow infiltration [1].

Two subtypes of HSTCL are described in the last World Health Organization (WHO) classification: a more common form expressing γδ T-cell receptor (TCR) chain and a rarer second one expressing αβ TCR chain. Both present similar onset and clinical course and the αβ subtype of HSTCL is considered an immunophenotypic variant.

HSTCL is a highly aggressive malignancy associated with a poor prognosis, because the results obtained by conventional chemotherapy usually are disappointing, with a median overall survival barely exceeding 1 year [2]. Given the rarity and the aggressiveness of the disease, several investigators have explored the use of high dose chemotherapy supported by autologous stem cell transplantation (SCT), without drawing any definite conclusions [3,4].

Allogeneic SCT (BMT) has a well established role in the treatment of otherwise incurable malignancies; in relapsed or refractory peripheral T-cell lymphoma, alloSCT enables to achieve a long-term remission in nearly 40% of the patients [5].

In patients affected by HSTCL there are anedoctal reports and small case series reporting beneficial effect of the allografting procedure, using HLA identical sibling or matched unrelated donors (MUD) [6–8].

In this report we describe, probably, the first case of refractory HSTCL to a previous autologous SCT and successfully rescued by a haploidentical allogeneic stem cell transplant (Haploidentical-SCT).

2. Case report

A 48-year-old man, without any relevant past medical problems and no social/physiological abnormalities, was referred to our service in May 2012 with fever, fatigue, weight loss, sweating and abdominal pain. He showed a considerable hepatomegaly (extending for 8 cm below the right costal margin) and

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splenomegaly (extending for 14 cm below the left costal margin). Laboratory data showed: haemoglobin level 11 g/dL, platelet count 72×10^9/L, white blood cell count 3.5×10^9/L with neutropenia (0.96×10^9/L) without morphological abnormalities; AST 184 IU/L and ALT 128 IU/L (normal values 10–40 IU/l); Lactate-dehydrogenase 4390 IU/L (normal < 500 IU/L). Serologic test for toxoplasmosis, cytomegalovirus, EBV, HIV, hepatitis, herpesvirus were negative.

Bone marrow analysis revealed the presence of 15% of cells with morphological aspect of medium-size lymphocytes with agranular cytoplasm and irregular shaped nuclei with nucleoli.

The flow cytometric immunophenotyping analysis of the bone marrow cells was positive for CD3 bright, TCR alpha-beta, CD2, CD16, CD56 and negative for CD4, CD8, CD5 and CD20.

TCR gene arrangement was studied by PCR analysis on marrow sample and showed clonal restriction of αβ chain [9]. Cytogenetic analysis revealed a normal karyotype.

A liver biopsy depicted an abnormal lymphocytic infiltrate CD3 positive, CD 4 and CD 8 negative and with the same TCR αβ clonal restriction pattern (Fig. 1).

A computed tomography (CT) was made for completing the work-up and showed enlarged liver and a massive splenomegaly with compressive picture on the stomach and with stenosis of splenic vein and dislocation of the kidney. Cerebrospinal fluid analysis was negative. All these findings were diagnostic of hepatosplenic αβ T cell lymphoma, stage IV B.

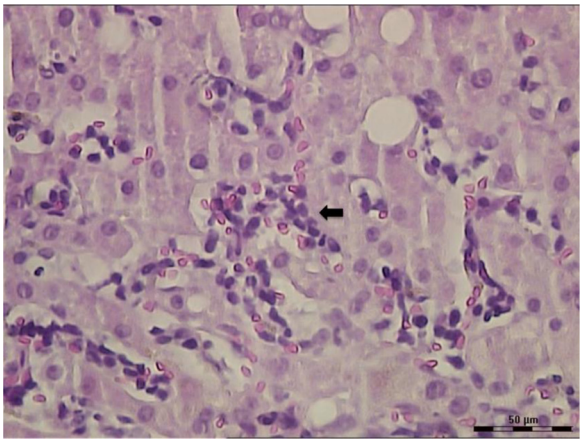

Fig. 1. Liver biopsy demonstrating a monomorphic, mostly intrasinusoidal, lymphoid infiltrate (arrow) composed of small to medium size cells (H&E stain, 500 ×).

The patient was started on induction chemotherapy containing cyclophosphamide, vincristine, etoposide, doxorubicin and prednisone (CHOEP) plus central nervous (CNS) prophylaxis with methotrexate and steroid. After the first cycle the patient's clinical picture did not improved, with persisting hepato-splenomegaly and liver dysfunction; therefore, we decided to intensify the treatment protocol with the Hyper-C-HIDAM regimen (cyclophosphamide 300 mg/m^2 days 1–3 plus high-dose cytarabine 2 g/m^2 bid days 1–3 and methotrexate 2000 mg/m^2 for 24 h of continuous infusion). After three courses a partial remission (PR) was achieved, with reduction of spleen size but persistence of neoplastic marrow involvement. During the fourth course of Hyper-C-HIDAM the patient was submitted to peripheral blood stem cell (PBSC) mobilization, with a yield of 6.8×10^6/kg. In October 2012, a high-dose conditioning therapy (FEAM) was begun with fotemustine (150 mg/m^2 −7, −6), etoposide (100 mg^2/m^2 −5, −4, −3, −2), cytarabine (200 mg^2/m^2 −5, −4, −3, −2) and melphalan (140 mg/m^2 −1), followed by reinfusion of autologous PBSC (3.40 CD34+ cells × 10^6/kg).

On day 30 after autoSCT the patient underwent a clinical and laboratoristic restaging: while total body positron emission tomography (PET) pointed out a complete response with the normalization of the hepato-splenomegaly, the bone marrow aspirate revealed the persistence of an abnormal lymphoid population with the same immunophenotypic profile (7% of cells).

Considering the disease persistence, a decision was made to perform an allogeneic stem cells transplant with a non myeloabtive conditioning (NMA). Since the patient had neither sibling nor voluntary donors it was established to carry out a HLA-haploidentical SCT from his daughter. Unfortunately, just a week before starting the preparative regimen, lymphoma progressed with an increasing splenomegaly, worsening of pancytopenia and increasing of the pathologic lymphoid cells in the marrow (70% of cells). Having evidence of the lymphoma's refractoriness and considering the patient's young age we re-scheduled our initial program towards a myeloablative conditioning regimen containing thiotepa (5 mg/kg −6, −5 days), Busulphan (3.2 mg/kg −5, −4, −3 days) and Fludarabine (30 mg/m^2 −7, −6, −5, −4 days), with reinfusion of 2.66×10^6/kg of CD 34+ bone marrow stem cells.

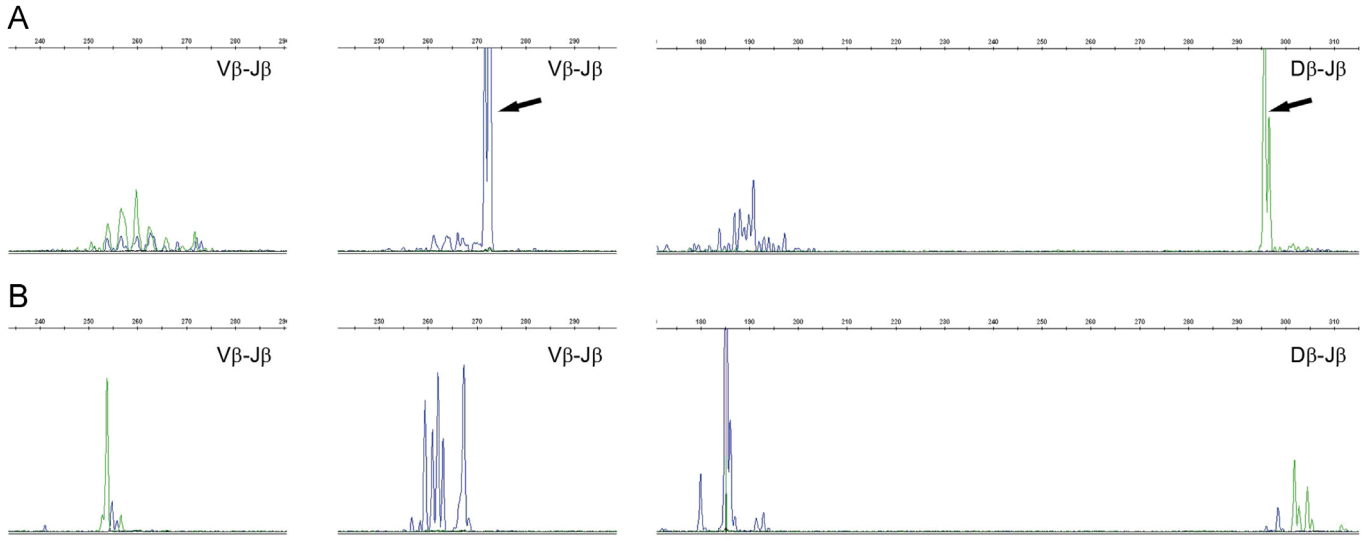

Fig. 2. PCR analysis of TCRβ gene rearrangement using BIOMED-2 protocol. Genescan clonality profiles of bone marrow aspirates at diagnosis (A) and after allogeneic stem cells transplantation (B). Clonal products (arrows) at diagnosis are no more visible at follow up after allogeneic transplantion and a different oligoclonal pattern emerge.

Graft versus host disease prophylaxis included tacrolimus, mycophenolate mofetil and post transplant cyclophosfamide (50 mg/kg on days +3 and +4) as previously proposed by Baltimora's group.

Engraftment post SCT was achieved successfully with complete recovery of hematologic blood count cells at day +18. Chimerism evaluation at day +28 revealed full donor chimerism, which was confirmed also at days +60 and +90, with contemporary demonstration of immunophenotipic complete remission at bone marrow aspirate. Patient did not show any sign of acute graft versus host disease (GVDH). The only one acute complication was an episode of hemorrhagic cystitis secondary to BK virus reactivation, successfully treated with cidofovir. Six months after transplant, during tapering of immunosuppression, limited chronic GVHD of skin and eyes developed, requiring a brief course of steroid plus UV-B applications; calcineurin inhibitors were substituted with low dose rapamycin.

After a follow up of 18 months patient is in good clinical conditions, in persisting complete remission as established both by PET and CT scan. Moreover the TCR αβ molecular analysis shows an oligoclonal pattern fully distinct from which manifested during the disease (Fig. 2).

3. Discussion

In this paper, we report the experience on a patient affected by a αβ variant of hepatosplenic T cell lymphoma, with rapid progression after autologous stem cell transplant and successfully rescued with a haploidentical transplant. Some important considerations might come up from our report.

First, the clinical course of the disease confirmed the dismal outcome of this subtype of lymphoma with conventional chemotherapy.

We started with a CHOP regimen but after the first cycle we had to shift the therapeutic approach towards a salvage regimen. We administered four cycles of hyper-C-HiDAM protocol, a therapeutic scheme containing hyperfractionated cyclophosphamide plus high-doses of Ara-C and methotrexate [10] followed by autoSCT. This approach is reported being effective for patients with aggressive NHL refractory to first-line anthracycline-containing regimens. A partial remission was obtained at the end of the program. However, as previously reported in PTCL [11,12], only the achievement of complete remission after induction therapy is a strong predictor of long term survival; thus, in this category of patients with a high risk of disease recurrence the general recommendation is to proceed rapidly to an allogeneic transplant. Unfortunately the major problem is related to the aggressiveness of the underlying disease, that does not allow to have enough time to find a suitable donor and to proceed to transplantation.

Considering the disease's aggressiveness and the lack of related or unrelated full match HLA donor; we decided to proceed anyway using the haploidentical daughter, despite the very few cases reported on the literature about the haplo transplants in this particular subtype of lymphoma.

Historically, alloSCT from HLA-haploidentical relatives has been limited by an unacceptably high non-relapse mortality, due to high rates of graft rejection and GVHD [13].

T-cell depletion of the donor graft represented a step forward in the haplo setting, but it required a high level of expertise in laboratory techniques [14].

Recently, the Baltimora and Seattle groups have pioneered a method to selectively deplete alloreactive cells in vivo by administering high doses of cyclophosphamide immediately post haplotransplant (PT/Cy) after a nonmyeloablative conditioning regimen. This approach resulted in a very low NRM, due to low incidences of GVHD and infectious complications [15]. In the previous years several studies [16–18] have confirmed the encouraging results of the haploidentical PT/Cy strategy. This alternative source with haploidentical donor is growing as a valid alternative option if a matched related donor is not rapidly available.

At the beginning our strategy was to follow the Baltimora's original scheme; however, given the very fast disease progression, we decided to change the type of pre-transplant conditioning therapy. We chose a myeloablative regimen with Thiotepa, Bufulsano and Fludarabine, in an attempt to achieve a better disease control in a patient with a well established refractory malignancy [19].

Allogeneic transplantation with myeloablative conditioning in peripheral T-cell lymphoma is a potentially curative option [20], but it is associated with a high treatment-related mortality (TRM), in particular after a failed autoSCT [21].Our patient at the time of transplant was in a relatively young age, in good clinical conditions, and without significative comorbidities (Sorror score 0), despite disease progression and previous treatment.

For that reason, our primary objective was to provide maximal tumor cytoreduction using a myeloablative preparation regimen containing high doses of Thiotepa and Busulphan in order to obtain a better disease control. The efficacy of this treatment was proved by the demonstration of complete remission at the day +60 (no spleen and liver activity on PET scan and the absence of marrow monoclonal infiltrate).

Finally, as previously reported [22] in other subtypes of peripheral T cell lymphomas, the persistence of complete remission after allografting corroborates the perception that a graft-versus-T cell lymphoma effect may play a role in the curative potential of alloSCT.

Focusing on the clinical history of the patient, we observed a rapid disease progression few weeks after conventional chemotherapy and also after autologous transplant; on the contrary we did not reveal any sign of any molecular relapse after more than one year of follow-up post haploidentical transplant, as demonstrated by the oligoclonal TCR pattern.

In conclusion, this report confirms that management of HSTCL refractory to conventional chemotherapy is still challenging. Some evidence suggested that haploidentical-SCT can activate an effective graft-versus lymphoma also in chemoresistant disease. This approach could offer a valid and safety alternative strategy in patients with neither a HLA-matched sibling or unrelated donor.

Conflict of interest

None of the authors has to declare a conflict of interest.

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