



Research Article

# How Far Can We Go? Tailoring Treatment in Advanced Stage Mycosis Fungoides/Sezary Syndrome

**Novelli Silvana<sup>1\*</sup>, Osuna-Gomez Ruben<sup>2</sup>, Narvaez Camila<sup>1</sup>, Mulet Maria<sup>2</sup>, Ortiz M Angels<sup>3</sup>, Esquirol Albert<sup>1</sup>, Martino Rodrigo<sup>1</sup>, Mozos Anna<sup>4</sup>, Sierra Jorge<sup>1</sup>, Garcia-Muret Pilar<sup>5</sup>, Vidal Silvia<sup>2</sup>**

<sup>1</sup>Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

<sup>2</sup>Inflammatory Diseases, Institut de Recerca de l'Hospital Sant Pau (IB-Sant Pau), Barcelona, Spain

<sup>3</sup>Immunology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

<sup>4</sup>Pathology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

<sup>5</sup>Dermatology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

**\*Corresponding Author:** Novelli Silvana, Hematology Department, Hospital de la Santa Creu i Sant Pau, Carrer Mas Casanovas 90, 4<sup>th</sup> floor, 08041-Barcelona, Spain

**Citation:** Silvana N, Ruben O-G, Camila N, Maria M, Angels OM, et al. (2022) How Far Can We Go? Tailoring Treatment in Advanced Stage Mycosis Fungoides/Sezary Syndrome. Ann Case Report. 7: 1061. DOI: 10.29011/2574-7754.101061

**Received Date:** 23 November 2022; **Accepted Date:** 28 November 2022; **Published Date:** 30 November 2022

## Abstract

Despite the improvement in therapy in most of the non-Hodgkin lymphomas, the scenario for advanced-stage mycosis fungoides/Sezary syndrome remains unmodified. Allogeneic stem cell transplantation is still the best option to maintain a durable response, but it requires previous good control of the disease, and it is associated with several complications which could be related to therapies.

Here we report a clinical case that pictures all the critical aspects of this rare and aggressive lymphoma: diagnosis and classification, selection of therapy, decisions based on comorbidities and tumoral modifications, and disease monitoring during therapies.

We found that, besides comorbidities and tumor characterization, the detection of tumoral cells and other immune cells by flow cytometry along the disease could help to improve therapy selection and also to understand disease evolution.

**Keywords:** Allogeneic stem cell transplantation; Cutaneous T cell lymphoma; Flow cytometry; Immunotherapy

## Introduction

Advanced stage mycosis fungoides/Sezary Syndrome is T-cell neoplasia with a reduced chance of cure even with recently approved new drugs [1-3]; it is associated with short disease-free

survival and overall survival probability, and the only potentially curative option is allogeneic stem cell transplantation (alloSCT). [4] Sequencing therapies to achieve the best response pre-allogeneic stem cell transplantation is as important as considering the potential modifications on immune system modulation that might impact the transplant outcomes. [5-8] Assessing tumor burden by direct skin examination, PET-CT, and flow cytometry

are the classic established methods to evaluate the disease response to therapies. [9] Still, new drugs such as anti-CCR4 and CD30 monoclonal antibodies require in-depth immunotypic analysis of normal and neoplastic populations to understand our patients' evolution better.

From now on, we describe our effort to take a young patient to an alloSCT on two occasions due to a very aggressive Sezary syndrome.

## Materials and Methods

Clinical and therapeutic information of the patient was collected from the clinical record. Peripheral blood samples were collected and processed for the analysis of leukocytes, including Sezary cells and T reg. Samples were acquired and analyzed with the MACSQuant Analyzer 10 flow cytometer (Miltenyi Biotec).

Peripheral Blood processing for Sezary cells and Treg monitoring briefly, 100  $\mu$ L of blood were washed with 2 mL of PBS. The pellet was stained with a panel of antibodies: CD25-BV421 (BD), CD4-Viogreen (Miltenyi Biotec), CD127-FITC (Miltenyi Biotec), CCR4-PE (Biolegend), CD8-Percp (Biolegend), CD3-PECy7 (Biolegend), CD14-APC (Immunotools), CD19-Percp (Biolegend), TRBC1-FITC (LSBio) y CD7-PE (Immunotools). Data acquisition and analysis was performed on a MACSQuant Analyzer 10 flow cytometer (Miltenyi Biotec). For data analysis, single cells were analyzed to select lymphocytes based on their morphology by forward- versus side-scatter (FSC-SSC) dotplot. By combining anti-CD3, anti-CD8 and anti-CD4, we identified CD3+ CD8+ (CD8+ T cells) and CD3+ CD4+ (CD4+ T cell). Regulatory T cells (Tregs) were defined by CD25 + CD127 low expression on CD4+ T cells. Then, B cells were defined by CD19 expression on lymphocytes. Monocytes were detected by CD14 expression and neutrophils by CD16. Each of population was divided based on CCR4 expression. The cutoff for CCR4 positivity on cells was determined using fluorescence minus one (FMO). The percentage of CCR4 positive cells in each subset were obtained using FlowJo version 10 (FlowJo, Ashland, OR).

For the detection of Sezary cells, live single cells were analyzed to select lymphocytes based on their morphology by forward- versus side-scatter (FSC-SSC) dotplot. By combining

anti-CD3, and anti-CD4, we identified CD3+ CD4+ (CD4+ T cell). Sezary cells were defined by the lack of CD7 on CD4+ T cells. Then, cells were divided based on TRBC1 expression. The percentage of TRBC1+ CD4+ T and TRBC1- CD4+ T cells were obtained using FlowJo version 10 (FlowJo, Ashland, OR).

## Results

A previously healthy 40-year-old male was initially diagnosed in April 2018 with a peripheral T-cell lymphoma (PTCL) not otherwise specified stage IV-A. He was refractory to conventional chemotherapy schemes (CHOP, ESHAP). After initial therapy, He presented erythroderma accompanied by plaques and patches distributed predominantly in the upper body, never documented before. A complete blood count (CBC) revealed a peripheral blood lymphocytosis. Flow cytometry demonstrated a CD4<sup>+</sup> lymphocytosis (90%), with CD2<sup>+</sup>, CD3<sup>+</sup>, CD4<sup>+</sup>, CD7<sup>-</sup>, CD8<sup>-</sup>, CD26<sup>-</sup> population, and Sezary cells in the blood smear. The patient underwent a skin biopsy that showed an atypical inflammatory infiltrate in the upper dermis, with a CD3<sup>+</sup>, CD4<sup>+</sup>, and CD7<sup>-</sup> CD8<sup>-</sup> lymphoid population, T-cell receptor polymerase chain reaction (PCR) studies supported a clonal T-cell process in the skin and blood. These findings were consistent with Sezary Syndrome (SS) (stage IVA2; T4, N2, M0, B2). At that moment he was referred to our center for re-assessment. A next-generation sequencing (NGS) study using the Oncomine Myeloid Research Assay was performed on lymph node biopsy, which revealed a mutation in TP53 (c.610G>T, p.Glu204Ter) in 16,68%.

In April 2019 he received a low-dose scheme of Alemtuzumab for 5 weeks achieving a complete blood and skin response, but PET-CT revealed subcentimetric mildly hypermetabolic lymph nodes (axillar, cervical, retro-pectoral). At this point, given the low tumor burden, we proceed with a reduced-intensity HLA identical unrelated alloSCT conditioned with thiotepa-fludarabine-melphalan with post-alloSCT cyclophosphamide (PTCy) in July of 2019. He received sirolimus/tacrolimus for graft versus host disease (GVHD) prophylaxis. During the first 100 days, he developed suggestive symptoms of gastric GVHD, which delayed immunosuppression tapering. He relapsed 4.5 months after alloSCT with blood and skin involvement. Relevant information to each therapeutic approach is resumed in Table 1.

| <b>Chemotherapy</b>         | <b>Aza-Romi (pre 1st cycle)</b> | <b>Moga (pre 1st)</b> | <b>Moga (pre 2nd)</b> | <b>Moga(pre 3rd)</b> | <b>Moga (pre 4th)</b> | <b>after ICE + ECP</b> | <b>Interin BV+ECP (2nd cycle)</b> | <b>pre-2nd alloSCT</b> | <b>30 days post-alloSCT</b> | <b>90 days post-alloSCT</b> |
|-----------------------------|---------------------------------|-----------------------|-----------------------|----------------------|-----------------------|------------------------|-----------------------------------|------------------------|-----------------------------|-----------------------------|
| LDH (125-243 U/L)           | 391,0                           | 238,0                 | 287,0                 | 398,0                | 330,0                 |                        | 393,0                             |                        |                             | 218,0                       |
| Hemoglobin (g/L)            | 135,0                           | 131,0                 | 136,0                 | 149,0                | 136,0                 |                        | 120,0                             | 118,0                  | 74,0                        | 81,0                        |
| Platelets (x10e9/L)         | 174,0                           | 138,0                 | 145,0                 | 148,0                | 145,0                 |                        | 138,0                             | 92,0                   | 18,0                        | 17,0                        |
| Leukocytes (x10e9/L)        | 9,8                             | 6,6                   | 9,2                   | 7,6                  | 5,7                   |                        | 8,9                               | 8,2                    | 1,0                         | 4,1                         |
| Neutrophils(x10e9/L)        |                                 | 4,0                   | 7,2                   | 4,7                  | 1,6                   |                        | 3,5                               | 3,1                    | 0,5                         |                             |
| Monocytes(x10e9/L)          |                                 | 0,9                   | 0,6                   | 0,6                  | 0,7                   |                        | 0,6                               | 0,5                    | 0,2                         |                             |
| Eosinophils(x10e9/L)        | 5,0                             | 0,3                   | 0,4                   | 1,0                  | 1,3                   |                        | 0,1                               | 0,9                    | 0,1                         | 0,2                         |
| Lymphocytes(x10e9/L)        | 3,1                             | 1,2                   | 0,7                   | 1,2                  | 1,9                   |                        | 3,5                               | 4,2                    | 0,3                         | 0,2                         |
| CD4 (x10e6/L)               | 1906,0                          | 535,6                 | 140,4                 | 532,8                | 1221,2                |                        | 2751,5                            | 3040,1                 | 135,3                       |                             |
| CD8 (x10e6/L)               | 750,0                           | 325,0                 | 395,1                 | 315,6                | 370,1                 |                        | 591,5                             | 1029,0                 | 140,0                       |                             |
| T regulatory cells(x10e6/L) |                                 | 9,4                   | 27,0                  | 96,0                 | 14,3                  |                        | 1,2                               | 7,1                    | 16,5                        |                             |
| NK(x10e6/L)                 | 51,0                            | 34,3                  | 36,8                  | 12,2                 | 18,2                  |                        | 36,5                              | 26,2                   | 17,4                        |                             |
| B cell(x10e6/L)             | 175,0                           | 333,0                 | 136,0                 | 189,2                | 208,0                 |                        | 18,1                              | 10,5                   | 2,0                         |                             |
| <b>Disease Status</b>       |                                 |                       |                       |                      |                       |                        |                                   |                        |                             |                             |
| Blood (Sezary (x10e9/L))    | PD                              | PR                    | PR                    | NA                   | PD                    | PD                     | SD                                | PR                     | CR                          | CR                          |
| Skin                        | PD                              | PD                    | PR                    | NA                   | PR                    | PD                     | SD                                | PR                     | CR                          | CR                          |
| Nodes                       | PD                              | CR                    | NA                    | NA                   | PD                    | PD                     | SD                                | CR                     | CR                          | CR                          |
| <b>allo SCT Chimera</b>     |                                 |                       |                       |                      |                       |                        |                                   |                        |                             |                             |
| T cell donor chimerism      | 16%                             |                       | 38%                   | 20%                  | <5%                   | <5%                    | <5%                               | NA                     | 95%                         | 100%                        |

|                             |     |    |      |      |     |     |     |    |      |      |
|-----------------------------|-----|----|------|------|-----|-----|-----|----|------|------|
| Granulocyte donor chimerism | 95% |    | 100% | 100% | 90% | 90% | 90% | NA | 100% | 100% |
| GVHD                        | no  | no | no   | no   | no  | No  | No  | no | no   | yes  |

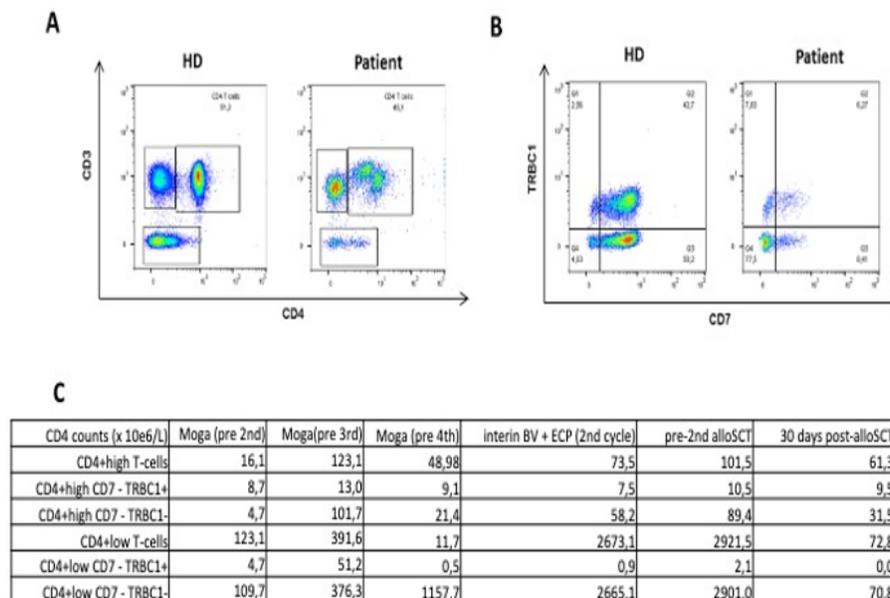
Acronyms: Aza-Romi (Azacytidine-Romidepsin), Moga (Mogamulizumab), ICE+ECP (ifosfamide carboplatin etoposide + extracorporeal photopheresis), haplo (haplidentical allogeneic stem cell transplantation), LDH (lactate deshydrogenase), alloSCT (allogeneic stem cell transplantation).

Immunosuppression was stopped with no clinical benefit. Because the tumor expressed CD30, brentuximab vedotin (BV) was administered, followed by a donor lymphocytes infusion (DLI); he received a second cycle of BV additionally with no response. Sezary cells persisted and erythroderma presented with severe pruritus. He also received additional cycles of gemcitabine, alemtuzumab, and a 2<sup>nd</sup> DLI with no response. Donor T-cells were 5% at this point, and there were no signs of GVHD. With the aim of arriving to a 2<sup>nd</sup> alloSCT he initiated romidepsin (14 mg/ m<sup>2</sup>) combined with azacitidine (75 mg/ m<sup>2</sup>) for three cycles. [10] Despite achieving a complete nodal response, there was a partial response on peripheral blood and skin. In the absence of GVHD, mogamulizumab [11] was started. He presented a partial blood and skin response, but after three cycles, we observed a nodal progression. We started ifosfamide-carboplatin-etoposide (ICE) and extracorporeal photopheresis (ECP) every 15 days. The reevaluation PET-CT scan showed FDG-avid nodes and persistence of Sezary cells on peripheral blood. A new lymph node and skin biopsy were performed, and both showed CD30

expression. Then BV was rechallenged, and after two cycles, the patient was in stable disease, and after four doses he was in partial response. ECP was never stopped. We considered that it was the right moment to proceed to a 2<sup>nd</sup> alloSCT. T regulatory cells were reduced after mogamulizumab but recovered before 2<sup>nd</sup> alloSCT.

The patient received a reduced-intensity haploidentical transplant from his mother conditioned with thiotepa-fludarabine-busulfan and with PTCy; he received GVHD prophylaxis with tacrolimus. He had respiratory syncytial virus Infection and covid19 pneumonia, which produced a chronic cough and a reduced ventilatory capacity.

The evolution of Sezary cells and normal CD4, CD8, T-regs, B-cells, monocytes, and neutrophils populations were analyzed pre, during, and post-therapy by multiparametric flow cytometry (mogamulizumab, ICE - ECP, BV- ECP and second alloSCT). Throughout the therapeutic history, we characterized the tumoral population in blood as CD3+ low CD4+ CD7 - TRBC1+, which disappeared after 2<sup>nd</sup> alloSCT. (Figure 1).



**Figure 1:** (A-B) Gating strategy and (C) percentage of TRBC1 in CD7-high and low CD4+ T cells. Acronyms: HD: Healthy Donor

He had a poor graft, and he needed G-CSF, erythropoietin, and platelet transfusions every ten days despite the use of thrombopoietin analogs. He received a CD34+ boost that led to a transient increase in all blood series, but he immediately developed a fast-progressing skin grade 4 GVHD which was controlled with ECP and lung GVHD, which was impossible to treat. Eleven months after 2<sup>nd</sup> alloSCT the patient died in CR due to a respiratory infection with grade 4 GVHD.

## Discussion

This case illustrates the complex evolution of a patient with SS. From the diagnosis of the disease with great inter and intra-patient clinical, biological, and molecular polymorphism, and the need to individualize management. It is known that 20-30% of MF/SS debut or progress into advanced stages (IIB-IVB), [12], and their prognosis drastically worsens, with survivals that do not exceed 4.7 years from stages IIB to IVB. [13] These patients require systemic treatment associated with skin-directed therapy. None of the options available for MF/SS are curative, with the exception of alloSCT. Patients are often treated with multiple sequential systemic therapies and eventually become refractory to all available agents. The objective in high-risk patients will be to achieve the best possible response to be able to perform alloSCT [14, 15].

Available and investigational therapies often have differential activity across disease compartments. This is an important element guiding treatment selection, along with disease subtype, patients' age, and presence of comorbidities, the extent of disease and staging, and availability of treatment.

We analyzed leukocytes, including Sezary cells and T regulatory cells (Tregs), to measure tumoral burden and check immune recovery after mogamulizumab. The evolution of tumoral cells and non-tumoral cells through therapy shows the impact of therapies on cell subsets; in this particular case was only helpful in measuring tumor burden. Acute GVHD is mediated by mature effector T cells from the donor (graft) that become activated after encountering allo-antigens in the recipient (host). Chronic GVHD, characterized by aberrant immune responses to both autoantigens and allo-antigens, occurs later and arises from a failure to develop tolerance after HSCT. Tregs suppress auto and alloreactive immune responses and mediate immune tolerance. [16] Despite Treg recovery before alloSCT our patient developed mild GVHD in the begging leading us to think that tissue damaging factors (infections, cytotoxic effects of chemotherapy), other innate immune cells, costimulatory pathways and immune cell signaling were the conditioning factors to GVHD progression.

We have noticed that sensitivity to BV, even after initial refractoriness, might be influenced by previous therapies (mogamulizumab, ECP, etc.), and this might be an important area of research.

## Conclusion

The purpose of future research in MF/SS is to contribute to establishing biomarkers and strategies that enrich individualized management, thus reducing toxicities and improving the quality of life of patients.

## Acknowledgements

We have to express our appreciation to RPR for sharing his clinical information.

## Consent for publication

Written informed consent was obtained from the patient to publish this case report and any accompanying information. This report has been performed following the Declaration of Helsinki.

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