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Molecular Remission Through Donor Lymphocyte Infusion in Post-Transplant Secondary Myelofibrosis: Managing Early Relapse Signs

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Abstract **Case Report**

Symptomatic myelofibrosis (MF) often requires allogeneic hematopoietic stem cell transplantation (allo-HSCT) for a potential cure, but relapse and graft-versus-host disease (GVHD) remain critical post-transplant challenges. Here, we present the case of a 45-year-old woman with polycythemia vera who developed secondary MF and underwent haploidentical allo-HSCT. A preemptive donor lymphocyte infusion (DLI) at month 29, following signs of relapse, restored donor chimerism and reduced the JAK2 mutation, achieving molecular remission. Mild chronic GVHD was effectively managed. This case highlights the utility of MRD and chimerism monitoring and the efficacy of preemptive DLI in secondary MF.

Keywords: Donor lymphocyte infusion, secondary myelofibrosis, polycythaemia vera, JAK2, chimerism monitoring, MRD.

INTRODUCTION

Myelofibrosis is a myeloproliferative neoplasm characterized by reticular fibrosis of the bone marrow associated with a myeloid metaplasia of both liver and spleen. The JAK2-V617F mutation is acknowledged to be a recurrent mutation in myelofibrosis. Myelofibrosis may be primary or secondary to polycythaemia vera (PV) or essential thrombocythaemia. A diagnosis is frequently established during the chronic phase; however, the disease progression can result in acceleration or an acute transformation [1]. Despite the advent of novel therapeutic modalities, allogeneic transplantation (AlloHSCT) remains the only potentially curative intervention for myelofibrosis [2]. However, AlloHSCT procedure is associated with a risk of transplant related mortality (TRM) and the identification of eligible patients is not a straightforward process [3]. The decision to proceed with alloHSCT is based on the recommendations of the European Group for Blood and Marrow Transplantation (EBMT)/European Leukemia Net (ELN), which include a patient age of less than 70 years and a DIPSS score of intermediate-2 or high risk [4].

Disease relapse following transplant is another risk following this procedure and remains a significant concern. In such cases, medical treatment is often ineffective and toxic. A second transplantation may be a potential option, but carries a significant risk of toxicity and mortality [5]. One principal method of circumventing this scenario is the utilisation of preemptive donor lymphocyte infusions (DLI), which appear to be more efficacious when the tumour burden is minimal [6]. This intervention is from now on possible thanks to NGS and chimerism monitoring.

CASE REPORT

We present the case of a 45-year-old woman who was monitored for hypertension but had no other significant medical history.

In 2001, a complete blood count revealed the presence of polycythemia. Further tests revealed a JAK2 V617F mutation. A bone marrow biopsy demonstrated the absence of fibrosis. The diagnosis of PV was thus confirmed. The patient started cytoreductive treatment with hydroxyurea, in addition to low-dose aspirin. The patient undertook Hydroxyurea therapy until 2017, when anaemia developed. Further investigation led to a bone marrow aspiration, which revealed an excess of blasts at 8% and a chromosome 12p deletion in cytogenetics. The

therapeutic approach was to discontinue the cytoreductive treatment.

Subsequently, the patient reported increased fatigue, and splenomegaly on physical examination. Laboratory tests indicated thrombocytosis. A bone marrow biopsy was then performed, revealing marrow fibrosis. The diagnosis of myelofibrosis secondary to PV was thus confirmed. Consequently, cytoreductive therapy was resumed while awaiting the allogeneic transplant procedure. The patient did not have a 10/10 HLA matched donor but her son was haplo-identical.

The patient was admitted to the bone marrow transplantation unit on 25 May 2018. Myeloablative conditioning regimen comprised Thiotepa-busulfan-fludarabine (TBF-MAC). Transplant was performed on 30 May 2018 with bone marrow as graft source. The CD34+ cell dose was 2.55 x 10^6/kg. Cyclosporine A was initiated on the day prior to transplantation (day -1) in order to prevent graft-versus-host disease (GVHD), in addition to mycophenolate mofetil. Furthermore, post-transplant cyclophosphamide was administered on days 3 and 4. Neutrophil engraftment occurred on day +19, with platelet engraftment following on day +33. There were no indications or symptoms of GVHD. No further complication issued during the remainder of hospitalization. She was discharged from hospital on day +40 and regularly followed up in outpatient consultations.

During the follow-up, the patient exhibited signs of renal insufficiency. The examination revealed the presence of thrombotic macroangiopathy, which led to the decision to discontinue cyclosporine. A course of corticosteroids was initiated (1mg/kg/day).

On day +60, a tapering of corticosteroids was initiated, with the initiation of tacrolimus. An initial chimerism assessment was conducted, revealing host chimerism < 0.1%. Bone marrow biopsy was consistent with complete remission, without blast excess nor myeloproliferative pattern. On day +90, the patient had recovered her renal function, and the corticosteroids were tapered.

On Day 123, the patient reported the presence of chronic graft-versus-host disease (cGVHd) affecting the eyes, skin, and genital areas, all of which were observed to be at grade 1 (global chronic GvHd scoring: Moderate). Steroid (Dose 1mg/kg/day) were resumed. The clinical course was favourable, and corticosteroids were discontinued on day +165.

On M+7, host chimerism rose to 0.18%. Consequently, PROGRAF was tapered and stopped. Over the following months, there was a progressive loss of chimerism, with values increasing from 0.64% at M+13 to 1.63% at M+17. At month 21, however, there was an increase in chimerism to 4.7%, accompanied by the reappearance of the JAK2 mutation with a variant allele frequency (VAF) of 1.8%.

At M+26, there was a continued progressive loss of chimerism, at 8.5%, accompanied by an increase in the variant allele frequency (VAF) of the JAK2 mutation, reaching 14%.

At M+28, the evolution was observed to be progressing towards the loss of chimerism at 9.87%. Consequently, it was decided at that time to perform a donor lymphocyte infusion (DLI). The CD3+ cell dose was 5 x 10^5/kg, administered at M+29 of transplant.

A few days later (9 days after DLI), the patient exhibited signs of grade 1 cGvHd of the oral cavity and genital organs, with typical lichen-plannus like features (chronic GvHd global score: Mild). Host chimerism decreased to 0.1% with an undetectable JAK2 mutation in blood samples.

Subsequently, the patient has been monitored every 6 months with chimerism and blood JaK2 VAF until 2 years after DLI. The most recent consultation was on 5 May 2024, at M+72 post-transplant and M+44 post-DLI. The patient continues to display symptoms of mild chronic GvHd, albeit remaining without systemic treatement (topic cyclosporine for the mouth symptoms). On the last blood test, there was no cytopenia, chimerism remained below 0.1%, and the JAK2 mutation was still undetectable (Figure 1).

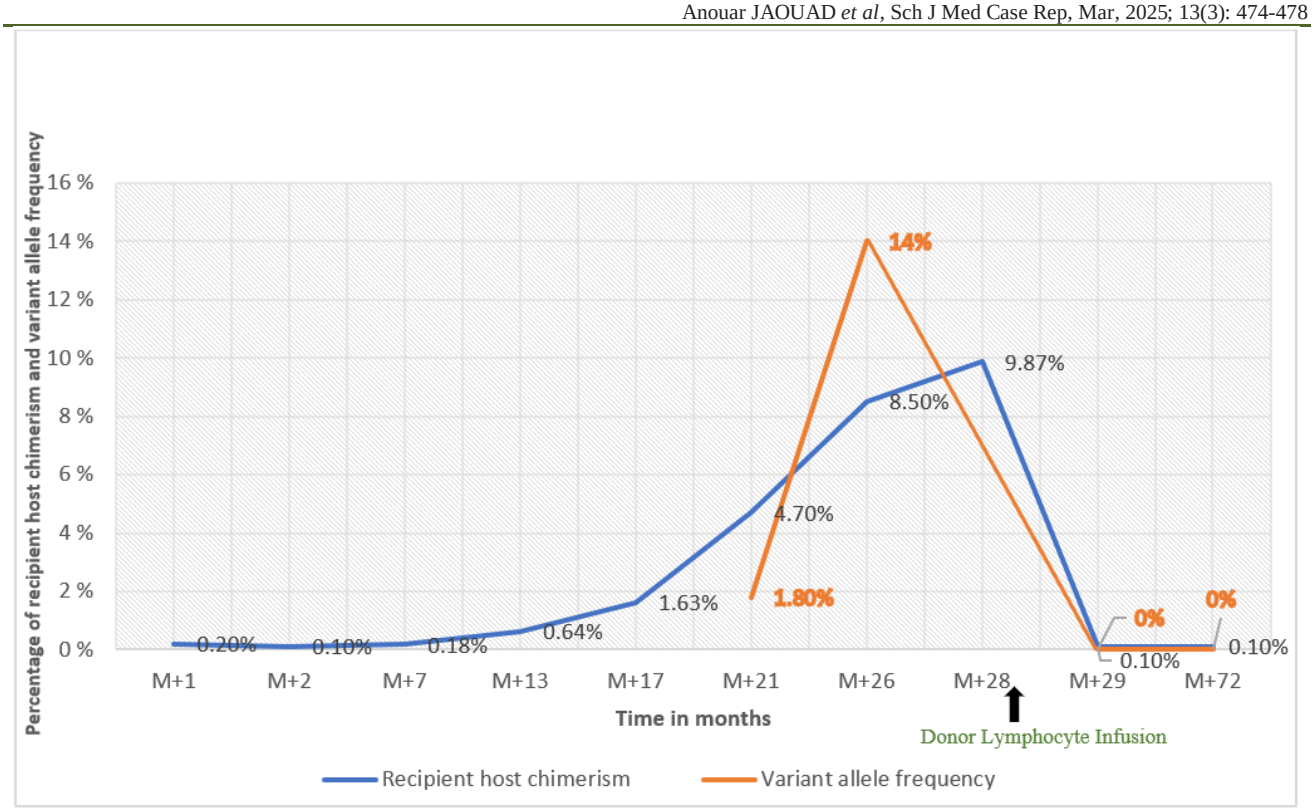

Figure 1: Monitoring of host chimerism and the Varient allele frequency of JAK 2 V617F

DISCUSSION

In this patient treated with allo-HSCT from an haplo-identical donor, the monitoring of chimerism and mutated jak2 VAF allowed us to precociously detect myelofibrosis relapse. A small DLI dose was sufficient to achieve a prolonged molecular response and complete donor chimerism with an acceptable toxicity and a preserved quality of life at > 5 years from alloHsCT.

The median survival of secondary myelofibrosis is 9 years, with mortality primarily associated with progression to acute leukaemia. A review of the literature reveals that 15 to 30% of patients experience a relapse after HSCT with a median of seven months [7,8]. However, later relapses have also been observed with a cumulative incidence of 14% over five years [9].

As previously outlined, relapse represents a significant mortality factor. However, graft-versus-host disease (GVHD) represents another significant mortality factor in allogeneic transplant patients, particularly given that these patients develop GVHD more frequently than those with other haematological diseases. However, recent studies have indicated the existence of a graft-versus-myelofibrosis effect, whereby the onset of GVHD symptoms may be associated with this phenomenon. We therefore describe the correlation between the appearance of GVHD symptoms and the reduction of Jak2 VAF [10].

In contrast to the prophylactic use of donor lymphocyte infusion (DLI), which is targeted at high-risk patients who have relapsed following an allogeneic transplant and who are generally characterised by unfavourable cytogenetics, chemoresistance, progressive disease, or measurable residual disease (MRD) positivity at the time of the transplant, the role of preemptive DLI after an allogeneic transplant allows for the control of mixed chimerism or molecular progression, which is evaluated by MRD. This appears to be a good predictive marker of disease relapse [11].

Two major factors have been identified as predictive of the response to DLI: the aggressiveness of the underlying disease and the tumor burden [12].

The use of DLI in a preemptive strategy must always be carefully evaluated based on the associated risks, particularly acute and chronic GVHD. The most common and direct complications of DLI depend primarily on the initial dose of DLI, but also on the interval between the allogeneic transplant and the DLI [13]. DLIs act by boosting the graft-versus-leukemia (GVL) effect, which is mediated by the restoration of T-cell immunity and the reversal of its exhaustion. Both of these processes are critical for the response to DLI [14].

The European Society for Blood and Marrow Transplantation (EBMT) has issued guidelines for the use of preemptive donor lymphocyte infusion (DLI). It is recommended that DLI be administered to patients who do not present with active graft-versus-host disease

(GVHD) or uncontrolled infections. In the case of genoidentical or phenoidentical transplants, the recommended starting dose is 5 x 10^6 cells per kg. In the case of haploidentical transplants, a lower starting dose of 10^5 cells per kg is recommended, given the increased risk of GVHD. A further three to four doses of DLI may be administered at intervals of four to 12 weeks until the patient achieves minimal residual disease (MRD) negativity [15].

In the reported case, we describe a successful outcome of premptive DLI in a patient with secondary myelofibrosi, following a loss of response after haploidentical allogeneic transplant. The main complication was well-controlled mild GVHD.

Monitoring MRD and chimerism post-transplant is crucial for early detection of relapse and timely treatment adjustments. Regular MRD monitoring helps predict relapse and guide therapeutic decisions, while chimerism tracking ensures graft success and alerts to potential immune intervention. Preemptive Donor Lymphocyte Infusions (DLI) are preferred over curative DLI because they intervene at an earlier stage when the tumor burden is lower, leading to higher efficacy and reduced side effects, thereby improving the chances of maintaining remission.

This case provides two main pieces of information. Firstly, it demonstrates that a haploidentical allogeneic transplant can be a viable option for patients suffering from secondary myelofibrosis. Secondly, it illustrates that DLIs remain a suitable intervention in the event of relapse.

CONCLUSION

This case highlights the effectiveness of preemptive donor lymphocyte infusion (DLI) guided by chimerism and minimal residual disease (MRD) monitoring in managing relapse after haploidentical allo-HSCT for secondary myelofibrosis. The intervention achieved durable molecular remission with manageable mild chronic GVHD, underscoring the importance of early immune intervention and vigilant post-transplant surveillance. It also demonstrates that haploidentical transplantation, combined with timely strategies like DLI, offers a viable curative option for patients lacking matched donors. These findings emphasize the value of personalized, preemptive approaches to improve outcomes in myelofibrosis.

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