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# Responses and Survival under Pegylated Interferon α2a Treatment for Patients with Post-MPN Acute Myeloid Leukemia and Acute Panmyelosis with Myelofibrosis

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## Abstract

We report here for the first time the efficacy of pegylated interferon α2a (Peg-Ifn) as a therapy for patients with myelofibrosis and high blast counts. We treated four patients who were in an accelerated phase of myeloproliferative neoplasms or acute panmyelosis with myelofibrosis using only this drug. We observed two complete responses, one partial response and one case of stable disease. Two patients then underwent allogeneic stem cell transplantation. The overall survival time ranged from 13 to 41 months. For our patients, Peg-Ifn induced a high level of response and a longer survival period than expected despite the histo-pathological features and unfavorable karyotypes of the patients included.

**Keywords:** Acute leukemia; Karyotype; Myelofibrosis; Pegylated interferon; Survival

## Introduction

Leukemic transformations (LT) of a Philadelphia-negative myeloproliferative neoplasm (MPN) including polycythemia vera (PV), essential thrombocythemia (ET) or primary myelofibrosis (PMF) are rare events and portend a dismal prognosis, with a median overall survival (OS) not exceeding a few months. Various strategies have been used to improve patient outcomes, including hypomethylating agents and intensive chemotherapy combined with allogeneic hematopoietic stem cell transplantation (ASCT), which seems to be the more efficient approach [1-3].

Interferons have been used with success in acute myeloid leukemia (AML) during the induction, post-ASCT and maintenance phases. This treatment is less burdensome than classical chemotherapy because patients can administer the drug at home (no long hospitalization), sub-cutaneous injection can be used (less need for central venous catheter), there are few side effects (no concomitant therapy to reduce the symptoms), and patients do not need to undergo transfusion [4].

We report here our experience using Pegylated-Interferon (Peg-Ifn) α2a in four consecutive patients with high-grade myelofibrotic MPN-LT who were unfit for intensive chemotherapy and in whom we observed a high level of clinical and biological responses and impressive survival (Table 1).

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| **MPN type** | APM | ET | MF | MF |
| **Age at MPN diagnosis (y)** | 42 | 52 | 76 | 63 |
| **Sex** | F | M | M | M |
| **Mutational status** | 3 NEG | CALR+ | 3 NEG | 3 NEG |
| **Time to AML (y)** | nd | 26 | 0.7 | 12 |
| **ECOG at the time of AML** | 0 | 1 | 1 | 0 |
| **Biological parameters at the beginning of Peg-Ifn** | | | | |
| **Hemoglobin (g/L)** | 81 | 104 | 116 | 72 |
| **Leukocytes (giga/L)** | 2.4 | 35.9 | 31 | 12.1 |
| **Platelets (giga/L)** | 41 | 453 | 61 | 38 |
| **Circulating blasts (%)** | 19 | 10 | 19 | 9 |
| **BM blasts (%)** | 10 | 80 | 10 | 47 |
| **Grade of bone marrow fibrosis** | 3 | 3 | 2 | 3 |
| **Karyotype** | Unfavorable | Unfavorable | Unfavorable | Intermediate |
| **Treatment before Peg-Ifn** | None | None | Hydroxyurea | 3+7 regimen |
| **Duration of Peg-Ifn (m)** | 6 | 14 | 40 | 9 |
| **Hematological response (m)** | Complete (6) | Complete (12) | Partial (6) | Partial (6) |
| **Cytogenetical response (m)** | Complete (6) | Complete (12) | nd | nd |
| **Grade of bone marrow fibrosis at evaluation (m)** | 2 (6) | 2 (12) | nd | nd |
| **Global response (PMN-AML consensus) [12]** | ALR-C | ALR-P | ALR-P | SD |
| **ASCT** | Yes | Yes | No | No |
| **Survival from AML diagnosis (m)** | 26 | 18 | 41 | 13 |
| **Status** | Alive | Dead | Dead | Dead |
| **Etiology of death** | Na | Aspergillosis | cardiac insuffisance | aspergillosis |

3 NEG: triple negative; ALR: Acute leukemia response; AML: Acute myeloid leukemia; APM: Acute panmyelosis with myelofibrosis; C: Complete response; CALR: Calreticulin; ET: Essential thrombocythemia; MF: Myelofibrosis; na: Not applicable; nd: Not done; P: Partial response; SD: Stable disease; Peg-Ifn: Pegylated interferon α2a.
Karyotypes: case1 = 46,XX,t(X;3)(p22;q21-22)[15]/46,idem,add12p11[5] /46,XX[1]; case 2 = 46,XY, t(3;3) (q21;q26)[15]/46,XY[9] ; case 3 = 46,XY,+8[25]; case 4 = 47,XY,+der(18)t(6;18)(q2?6;q21)[18]/46,XY, t(6;18)(q2?6;q21)[9].
**Table 1:** Characteristics of the four patients treated with Peg-Ifn α2a

## Patients and Methods

We have extensive experience in the use of Peg-Ifn in our two centers and have treated more than three hundred patients with this drug. In cases of AML, patients should be treated as recommended by the French cooperative groups with intensive chemotherapy or azacitidine (adjusted to the age). If this is not possible, due to co-morbidities or patient preference, our locals recommendations are to propose Peg-Ifn α2a to patients with both AML and myelofibrosis (with fibrotic grade ≥2), regardless of the patient's performance status (0 to 2). These attitudes have been validated by clinicians belonging to five hospitals. Patients gave their oral agreement to receive this treatment.

## Results and Case reports

Case 1 is a 42-year-old female with pancytopenia and circulating blasts who was diagnosed with acute panmyelosis with myelofibrosis (APM) upon bone marrow biopsy (grade 3 fibrosis). Cytogenetic exams showed an unfavorable karyotype. Molecular testing showed no *JAK2V617F, calreticulin* or *MPL* mutations. After discussion with the patient, a strategy based on weekly injections of 135 µg of Peg-Ifn α2a was established. After 6 months of treatment with no adverse events reported, we obtained both hematological and cytogenetic complete remissions. The patient underwent a geno-identical ASCT and is still alive 26 months after diagnosis, with durable remission and without any symptoms of graft versus host disease (GVHd).

Case 2 is male who was diagnosed with ET in 1984 and is positive for a *calreticulin* type 2 mutation. He did not receive any treatment since his diagnosis. After 26 years, at 52 years of age, the patient presented with leukocytosis and circulating blasts. Bone marrow exams showed a grade 3 fibrosis with 80% blast infiltration and secondary AML with an unfavorable karyotype; the patient was then refused by clinicians for intensive chemotherapy. Peg-Ifn α2a was started at 135 µg weekly and then increased to 180 µg weekly because of a partial response (the patient experimented flu-like symptoms during the first month of increased dose). At 12 months, the patient achieved complete hematological and cytogenetical responses. An ASCT was then performed, and at d30, histological and cytogenetical complete remissions were obtained. The patient died three months after ASCT from aspergillosis.

Case 3 is a 76-year-old male with a triple-negative untreated PMF (with grade 2 fibrosis) who experienced an 8-month rapid progression of constitutional symptoms that revealed an accelerated phase disease (19% of circulating blasts and unfavorable karyotype). The patient was too old to receive a classical chemotherapy regimen. He received Peg-Ifn α2a 135 μg/week, with improvement of his general condition and a partial regression of clinical symptoms and transfusion dependency at 6 months. The patient wanted to continue his treatment because of his good tolerance (only transient asthenia and skin reactions at the injection site) and because no alternative drug was available. After 41 months of therapy, he died from heart failure.

Case 4 is a 63-year-old male who was diagnosed with secondary AML with 47% medullar blasts and an intermediate karyotype 12 months after the diagnosis of a grade 3 fibrosis triple-negative untreated PMF. After the initial failure of a 3+7 regimen, he received a weekly dose of 135 μg of Peg-Ifn α2a with no reported side effects. Clinical improvement was observed, and a partial hematological response was obtained after six months. He died from pulmonary infection after 13 months of therapy.

## Discussion

Leukemic transformations are highly adverse events that arise during the course of MPN and occur in 1–3%, 5–15%, and 10–20% in patients with ET, PV or PMF, respectively, after ten years. The prognosis is catastrophic, and ASCT is considered the only curative therapy available, though it is mostly given to younger patients, who can achieve complete remission [1-3]. In contrast, for older patients who are not candidates for ASCT, hypomethylating agents have been evaluated. In a cohort of 54 patients, azacitidine showed an overall response rate (ORR) of 38% and a median overall survival (OS) of 8 months in post-MPN AML and 11 months in post-MPN myelodysplastic syndrome (MDS) [2]. Six patients treated with decitabine obtained an ORR of 50%, with a median OS of 9.5 months in a phase 2 trial, whereas 14/34 (41%) patients were responders with a median OS of 11.8 and 10.5 months in post-MPN accelerated phase or AML, respectively [2,5]. No specific information is available on the efficacy of azacitidine in patients with AML and high-grade myelofibrosis. However, azacitidine induces a small benefit for patients with myelofibrosis [6].

Furthermore, Ruxolitinib, known as a non-specific JAK1 and JAK2 inhibitor, was recently shown to induce complete remission and increase survival in some patients, mostly in combination with low-dose cytarabine or azacitidine [7,8]. At the time of these cases, ruxolitinib has just begun to be prescribed and was available for patients with symptomatic myelofibrosis.

In contrast, direct blast toxicity has been reported as a consequence of the (i) reduced secretion of growth-promoting cytokines, (ii) stimulation of apoptosis, (iii) inhibition of cell proliferation and (iv) increased immunogenicity of the AML blast cells. The indirect antineoplastic effects are due to the stimulation of dendritic cells (DC), natural killer cells (NK) and T lymphocytes. The development of long-acting formulations of Peg-Ifn α2a and α2b have allowed both better tolerance and adherence to treatment, stable cytotoxic serum Ifn concentrations, and the ability to achieve adequate anti-leukemic control in some cases [2,9].

Furthermore, two case reports showed an excellent response in patients with post-MPN AML after treatment with Peg-Ifn α2a as the sole therapy [10,11].

We showed here the efficacy of using Peg-Ifn α2a as the sole therapy in highly myelofibrotic post-MPN AML or APM. We obtained (i) complete cytogenetical response despite an unfavorable karyotype, (ii) reduction of the intensity of bone marrow fibrosis despite initial high-grade fibrosis and (iii) patient fitness for successful ASCT, and (iv) an increase in survival from 13 to 41 months compared with less than 3 months, as reported in the literature. We also tested low-dose drugs in three other patients with post-MPN AML who were more than 80 years old or had performance statuses of 3, but all of them died within three months of treatment initiation.

## Conclusion

In our cases, Peg-Ifn permitted a long survival for patients with post-MPN AML, despite unfavorable karyotypes and high-grade myelofibrosis. At this time, when azacitidine and ruxolitinib are available and helpful in some cases but have not yet been tested in phase 2-3 trials, these four cases showed that Peg-Ifn α2a should also be considered as a potential active drug for these patients with an acceptable performance status.

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## References

1. Kennedy JA, Atenafu EG, Messner HA, Craddock KJ, Brandwein JM, et al. (2013) Treatment outcomes following leukemic transformation in philadelphia-negative myeloproliferative neoplasms. Blood 121: 2725-33.

2. Thepot S, Itzykson R, Seegers V, Raffoux E, Quesnel B, et al. (2010) Treatment of progression of Philadelphia-negative myeloproliferative neoplasms to myelodysplastic syndrome or acute myeloid leukemia by azacitidine: a report on 54 cases on the behalf of the Groupe Francophone des Myelodysplasies (GFM). Blood 116: 3735-42.

3. Lussana F, Rambaldi A, Finazzi MC, van Biezen A, Scholten M, et al. (2014) Allogeneic hematopoietic stem cell transplantation in patients with polycythemia vera or essential thrombocythemia transformed to myelofibrosis or acute myeloid leukemia: a report from the MPN Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 99: 916-21.

4. Anguille S, Lion E, Willemen Y, van Tendeloo VFI, Berneman ZN, et al. (2011) Interferon-α in acute myeloid leukemia: an old drug revisited. Leukemia 25: 739-48.

5. Badar T, Kantarjian HM, Ravandi F, Jabbour E, Borthakur G, et al. (2015) Therapeutic benefit of decitabine, a hypomethylating agent, in patients with high-risk primary myelofibrosis and myeloproliferative neoplasm in accelerated or blastic/acute myeloid leukemia phase. Leuk Res 39: 950-6.

6. Mesa RA, Verstovsek S, Rivera C, Pardanani A, Hussein K, et al. (2009) 5-Azacitidine has limited therapeutic activity in myelofibrosis. Leukemia 23: 180-2.

7. Eghtedar A, Vertovsek S, Estrov Z, Burger J, Cortes J, et al. (2012) Phase 2 study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including postmyeloproliferative neoplasm acute myeloid leukemia. Blood 119: 4614-8.

8. Tabarroki A, Sauntharajah Y, Visconte V, Cinalli T, Colaluca K, et al. (2015) Ruxolitinib in combinaison with DNA methyltransferase inhibitors: clinical responses in patients with symptomatic myelofibrosis with cytopenias and elevated blast(s) counts. Leuk Lymph 56: 497-9.

9. Krönig H, Kremmler L, Haller B, Englert C, Peschel C, et al. (2011) Interferon induced programmed death-ligand 1 (PDL1/B7-H1) expression increases on human acute myeloid leukemia blast cells during treatment. Eur J Haematol 92: 195-203.

10. Berneman ZN, Anguille S, van Marck V, Schroyens WA, van Tendeloo VF (2010) Induction of complete remission of acute myeloid leukaemia by pegylated interferon-alpha-2a in a patient with transformed primary myelofibrosis. Br J Haematol 149: 152-5.

11. Dagorne A, Douet-Guilbert N, Quintin-Roue I, Guillerm G, Couturier MA, et al. (2013) Pegylated interferon α2a induces complete remission of acute myeloid leukemia in a post-essential thrombocythemia myelofibrosis permitting allogenic stem cell transplantation. Ann Hematol 92: 407-9.

12. Mascarenhas J, Heaney ML, Najfeld V, Hexner E, Abdel-Wahab O, et al. (2012) Proposed criteria for response assessment in patients treated in clinical trials for myeloproliferative neoplasms in blast phase (MPN-BP): formal recommendations from the post-myeloproliferative neoplasm acute myeloid leukemia consortium. Leuk Res 36: 1500-4.