

Responses and Survival under Pegylated Interferon α 2a Treatment for Patients with Post-MPN Acute Myeloid Leukemia and Acute Panmyelosis with Myelofibrosis

Le Calloch R¹, Chauveau A², Boyer-Perrard F³, Dagherne A⁴, Luque Paz D⁵, Douet-Guilbert N⁶, Quintin-Roué I⁷, Guillerm G¹, Mercier M³, Berthou C¹, Ugo V⁵ and Ianotto JC¹

¹Service d'Hématologie Clinique, Institut de Cancéro-Hématologie, Hôpital Morvan, CHRU Brest, France

²Laboratoire d'Hématologie, Hôpital de La Cavale Blanche, CHRU Brest, France

³Service des Maladies du Sang, CHU Angers, France

⁴Service d'Hématologie, CH Saint-Brieuc, France

⁵Laboratoire d'Hématologie, CHU Angers, France

⁶Laboratoire de Cytogénétique, Hôpital Morvan, CHRU Brest, France

⁷Laboratoire d'Anatomo-pathologie, Hôpital Morvan, CHRU Brest, France

*Corresponding author: Ianotto JC, Service d'Hématologie Clinique, Institut de Cancérologie et d'Hématologie, Hôpital Morvan, CHRU Brest, 2 avenue Foch, 29609 Brest cedex, France, Fax: + 33 2 98 22 33 23, Tel: + 33 2 98 22 34 21, E-mail: jean-christophe.ianotto@chu-brest.fr

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Abstract

We report here for the first time the efficacy of pegylated interferon α 2a (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) α 2a 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 $\alpha 2a$.

Karyotypes: case 1 = 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 $\alpha 2a$

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 local recommendations are to propose Peg-Ifn $\alpha 2a$ 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 $\alpha 2a$ 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 $\alpha 2a$ 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 cytogenetic responses. An ASCT was then performed, and at d30, histological and cytogenetic 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 α 2a 135 μ g/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 μ g of Peg-Ifn α 2a 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 α 2a and α 2b 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 α 2a as the sole therapy [10,11].

We showed here the efficacy of using Peg-Ifn α 2a 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 α 2a should also be considered as a potential active drug for these patients with an acceptable performance status.

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