Non-adherence to treatment with cytoreductive and/or antithrombotic drugs is frequent and associated with an increased risk of complications in patients with polycythemia vera or essential thrombocythemia (OUEST study)

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ARTICLE

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ABSTRACT

The purpose of this study was to identify the incidence, causes and impact of non-adherence to oral and subcutaneous chronic treatments for patients with polycythemia vera or essential thrombocythemia. Patients receiving cytoreductive drugs for polycythemia vera or essential thrombocythemia were recruited at our institution (*Observatoire Brestois des Néoplasies Myéloprolifératives* registry). They completed a one-shot questionnaire designed by investigators (*Etude de l'Observance Thérapeutique et des Effets Secondaires des Traitements* study). Data about complications (thrombosis, transformation and death) at any time in the patient's life (before diagnosis, up until consultation and after the completion of the questionnaire) were collected. Sixty-five (22.7%) of 286 patients reported poor adherence (<90%) to their treatment with cytoreductive drugs and 46/255 /18%) also declared non-adherence to antithrombotic drugs. In total, 85/286 patients (29.7%) declared they did not adhere to their treatment. Missing an intake was rare and was mostly due to forgetfulness especially during occupational travel and holidays. Patients who did not adhere to their treatment were characterized by younger age, living alone, having few medications but a high numbers of pills and determining their own schedule of drug intake. Having experienced thrombosis or hematologic evolution did not influence the adherence rate. Non-adherence to oral therapy was associated with a higher risk of phenotypic evolution (7.3 *versus* 1.8%, *P*=0.05). For patients treated for polycythemia vera or essential thrombocythemia, non-adherence to cytoreductive and/or antithrombotic therapies is frequent and is influenced by age, habitus and concomitant treatments, but not by disease history or treatment side effects. Phenotypic evolution seems to be more frequent in the non-adherent group. (ClinicalTrials.gov #NCT02893410, #NCT02897297).

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Introduction

Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms (MPN) arising from the clonal expansion of a multipotent hematopoietic stem cell, causing deregulated proliferation of myeloid lineages. Therapeutic management of these chronic pathologies has two objectives: reduction of the thrombotic risk induced by blood hyperviscosity (short-term) and reduction of the risk of transformation into myelofibrosis or acute myeloid leukemia (long-term).[1] Available treatments are administered orally (hydroxycarbamide, pipobroman, anagrelide or ruxolitinib) or subcutaneously (pegylated interferon), usually in combination with antithrombotic drugs.

The problem of lack of adherence to treatment is likely as old as the practice of medicine, as indicated by Hippocrates' statement that "Patients often lie when they say that they take their medication". The World Health Organization reported that "improving patient adherence to chronic treatment should be more beneficial than any biomedical discovery".[2] Because anticancer drugs can significantly increase patients' survival, some cancers have become chronic diseases. Most drugs are costly, induce side effects and their efficacy frequently depends on the dose. For these reasons, adherence to cancer therapy is critical for an optimal benefit-risk ratio. Adherence to treatment has been extensively studied in asthma and diabetes, but few studies have approached this issue in patients with malignant diseases.[3]

The impact of non-adherence on the achievement of sustained remission was observed in patients with chronic myeloid leukemia in whom poor adherence to imatinib therapy may be the predominant reason for not reaching an optimal molecular response.[4-8] No "gold standard" exists to measure adherence, but a minimum of 90% drug intake was described as a good cut-off to discriminate treatment-adherent *versus* non-adherent patients.[7,9-11] In a meta-analysis, Noens *et al.* showed that the rate of treatment non-compliant patients with chronic myeloid leukemia was variable (from 3% to 56%), depending on the evaluation method. Adherence to hydroxycarbamide therapy has been studied in patients with sickle cell disease and appears suboptimal in most cases; better adherence was associated with improved clinical and economic outcomes.[12]

To the best of our knowledge, adherence to treatment has not been studied in PV or ET patients. We conducted a prospective clinical study to analyze adherence rates, reasons for non-adherence including the impact of previous complications and the influence of non-adherence on the clinical outcome of PV and ET patients.

Methods

Recruitment of patients

Between December 2014 and December 2015, adult patients followed for PV or ET at the *Institut de Cancéro-Hématologie* (CHRU of Brest, France) and treated with oral (group 1) or subcutaneous (group 2) cytoreductive therapies for more than 6 months were enrolled in the OUEST study (NCT02893410). All patients signed informed consent to participation in the study, which was approved by the regional authorities of the Ethics Committee "CPP Ouest V" dated 04/09/2014, pursuant to Article L.1121-1 of the Code of Public Health, and has been declared to the *Commission Nationale Informatique et Libertés* (CNIL) (N. 13809*03). We excluded patients treated for other MPN, patients who did not receive any treatment and those with physical or mental disabilities who were unable to consent and complete the questionnaire. These patients were identified by their inclusion in the "OBENE" observational registry for patients diagnosed with and treated for Philadelphia-negative MPN at our hospital (NCT02897297).

Questionnaire and data collected

This single-center prospective study was based on a closed questionnaire (with simple and multiple-choice questions) given to the patient at the end of a consultation or sent by e-mail. The questionnaire varied according to the route of administration of the cytoreductive drugs (oral or subcutaneous) (*Online Supplementary Figure S1*). The questionnaires were validated by both the Scientific and Ethical Committees of our hospital. A complete blood count was also performed at the time the questionnaire was administered.

The questionnaire was filled in by patients, the results of complete blood counts were collected and sent directly to the data analyzers. Consultants were not allowed to know which patients were or were not adherent to treatment.

Non-adherence to drug prescription was defined by at least three omissions of medication during the preceding month (representing ≥10% of the dose) for the group treated orally (group 1) and omission of at least one injection during the two preceding months for the subcutaneously treated group (group 2).

These definitions were chosen in accordance with the cut-offs identified by Marin *et al.*[6]

The patients were followed prospectively and new events (thrombosis, hematologic evolution and death) were recorded at the end of the study on February 1, 2017. At that point, the patients' identities were revealed to the consultants and the global analyses were performed.

Statistical methods

The responses were analyzed using conventional descriptive parameters. The response items were described in terms of frequency for qualitative responses and as the median ± the extreme values for quantitative answers. Statistical analyses were performed by the Clinical Investigation Center of Brest Hospital (INSERM CIC 1412) using SAS software (SAS, Brie Comte Robert, France). The data were compared using the chi-square test for qualitative parameters and non-parametric tests for quantitative parameters. A P value <0.05 was considered statistically significant. The risks of thrombosis and transformation were analyzed by calculating the hazard ratios between treatment-adherent and non-adherent patients.

Results

Description of the population study

We included 286 patients in the study: 136 (47.6%) with PV and 150 (52.4%) with ET as their initial diagnoses. The sex ratio was 0.74 in the whole cohort (164 males, 122 females). Of the 286 patients, 233 (81.5%) received their treatment orally (group 1) and 53 (18.5%) received it subcutaneously (group 2). All the patients' characteristics are summarized in Table 1.

Before completion of the questionnaire, most patients had experienced a complication related to their MPN: thrombotic events before or at diagnosis of MPN in 31.8% (74/233) and 18.9% (10/53) of patients in group 1 and 2, respectively, and between diagnosis and inclusion in the

study in 20.6% (48/233) and 28.3% (15/53); or phenotypic evolution in 12% (28/233) and 17% (9/53), respectively.

At the time of being administered the questionnaire, the patients' median age was 69.8 years old (range, 26-98.4) and the median follow-up since diagnosis had been 8.3 years (range, 0.5-36.9). In group 1, 163/233 patients (70%) took hydroxycarbamide with a median number of 10.7 pills per week whereas all patients but one in group 2 were receiving injections of pegylated interferon-α2a, in most cases every 3 weeks. Ongoing treatment was the first-line therapy in 72.3% and 22.6% of patients in groups 1 and 2, respectively. Antithrombotic drugs were administered to 217/233 patients (93.1%) of group 1 (78.3% low-dose aspirin) and 48/53 patients (90.6%) in group 2 (68.8% low-dose aspirin).

Characteristics of treatment non-adherent patients

Incidence of non-adherence

Table 1. Characteristics of the population studied.

Characteristics	Cohort	Group 1 Oral drugs	Group 2 SC drugs
Number of patients	286	233	53
Age at the time of consultation (y)	69.8	72.4	61.2
Sex ratio	1.34	1.4	1.12
Pathologies (ET/PV)	150/136	128/105	22/31
On-going treatment (n/%)			
Hydroxycarbamide	163 (57)	163 (70)	na
Anagrelide	37 (12.9)	37 (16)	na
Pipobroman	24 (8.4)	24 (10)	na
Ruxolitinib	9 (3.1)	9 (4)	na
Pegulated interferon α2a	52 (18.2)	na	52 (98,1)
Pegulated interferon α2b	1 (0.4)	na	1 (1,9)
Low dose aspirin	194 (72.9)	163 (74.8)	31 (64.6)
Vitamin-K antagonists	43 (16.2)	32 (14.7)	11 (22.9)
Clopidogrel	18 (6.8)	16 (7.3)	2 (4.2)
Associations of antithrombotic drugs	9 (3.4)	7 (3.2)	2 (4.2)
History of thrombotic events before diagnosis (n./%)	84 (29.4)	74 (31.8)	10 (18.9)
Cardiovascular risk factors (n/%)			
High blood pressure	131 (45.8)	112 (48)	19 (35.8)
Hypercholesterolemia	61 (21.3)	53 (22.8)	8 (15.1)
Tobacco use	26 (9.1)	20 (8.6)	6 (11.3)
Diabetes	22 (7.7)	20 (8.6)	2 (3.7)
Median follow-up before consultation (y)	8.3	7.6	11.9
Patients with complications from diagnosis to consultation (n/%)			
Thromboses	63 (22)	48 (20.6)	15 (28.3)
Hematologic evolutions	37 (12.9)	28 (12)	9 (17)
Median follow-up from consultation (y)	1.8	1.8	1.8
Patients with complications after completion of questionnaire (n/%)	35 (12.3)	32 (13.7)	3 (5.7)
Thromboses	18 (6.3)	16 (6.9)	2 (3.8)
Hematologic evolutions	8 (2.8)	7 (3)	1 (1.9)
Death	17 (5.9)	17 (7.3)	0
Non-adherence analyses (n%)			
Cytoreductive drugs	65 (22.7)	55 (23.6)	10 (18.9)
Antithrombotic drugs	46 (18)	33 (15.2)	13 (27.1)
Both	27 (9.4)	22 (9.4)	5 (9.4)
Total	85 (29.7)	67 (28.8)	18 (34)

ET: essential thrombocythemia; na: non-applicable; n: number; PV: polycythemia vera; SC: subcutaneous; y: years; %: percent.

Using the criteria of non-adherence defined in the *Methods* section (missing at least 3 doses in the preceding month for oral drugs or 1 injection in the 2 preceding months for subcutaneous drugs), 65/286 patients (22.7%) were considered non-adherent to their cytoreductive drug therapy. Non-adherence was more frequent in the orally treated group (group 1) than in the subcutaneously treated group (group 2): 55/233 (23.6%) and 10/53 (18.9%) in groups 1 and 2, respectively, P=0.46). All the characteristics are showed in Table 2.

Regarding compliance with antithrombotic drug therapy, 46/286 patients (16.1%) in the whole cohort declared that they did not adhere fully to their treatment. The patients in group 2 declared a higher rate of non-adherence to their antithrombotic drugs compared to the patients in group 1 [13/53 (27.1%) *versus* 33/233 (15.2%), respectively, P=0.055]. In both groups, patients who were non-adherent to their cytoreductive drug treatment were also less adherent to their antithrombotic therapy compared to patients who were adherent to their cytoreductive drug treatment [26/65 (40%) *versus* 20/221 (9%), $P<10^{-7}$; ORR=6.64, 95% CI: 3.22-13.94].

In total, 85/286 patients (29.7%) were non-adherent to either cytoreduction or antithrombotic drugs and 27/286 to both treatments (9.4% of the total cohort or 31.8% of the non-adherent patients).

In both groups, the number of treatment omissions was close to the threshold defining non-adherence (around 10% of intake omissions) for most patients (96%) while the remaining 4% had very poor adherence to treatment (≥20%).

Analysis of the cohort

To tease out the characteristics of treatment non-adherent patients, we then analyzed the responses of these patients to cytoreductive drugs (n=65).

In the whole cohort, non-adherent patients were younger (68.1 *versus* 70.7 years, P=0.007), more frequently male (1.1 *versus* 0.66, P=0.07), taller (172 *versus* 165 cm, P=0.004) and heavier (74 *versus* 69 kg, P=0.01). The differences in height and weight were probably not only due to the gender bias because treatment non-adherent patients remained significantly taller even when only male patients were analyzed, (176 *versus* 173, P=0.002). This was not true for female patients. Furthermore, in the treatment non-adherent group there was a higher proportion of patients choosing their own drug intake schedule (55.4 *versus* 34.8%, P=0.003), a lower proportion of patients following a fixed intake schedule (64.6 *versus* 83.7%, P=0.0008) and fewer polymedicated patients (67.7 *versus* 79.2%, P=0.05). Interestingly, diabetic patients were significantly more adherent to their cytoreductive treatment [21/221 (9%) *versus* 1/65 (1.53), P=0.03; ORR=6.69, 95% CI: 1.03-281.86].

Since groups 1 and 2 had different rates of compliance, we analyzed the characteristics of the treatment non-adherent patients for each group.

In group 1, treatment non-adherent patients were younger than adherent patients (66.6 *versus* 73.4 years old; P=0.0013), more frequently determined the pill intake schedule themselves (52.8% *versus* 33.7%; P=0.029), dispersed their pill intake through the day instead of grouping the pills together (30.9% *versus* 10.8%; P=0.0003) and had fewer drugs to take (70.9% *versus* 82.5%; P=0.06). For group 2 patients, the only significant difference concerned

the dose of interferon: treatment non-adherent patients had higher doses (81.5 versus 46.5 μg/week, *P*=0.05).

Organizing pills according to intake schedules (drug diary) or having someone to remind the patients when to take their drug did not improve adherence. For both groups, having experienced thrombosis or phenotypic evolution did not modify the adherence to treatment. In the subpopulation of patients treated for ET, no significant association was found between non-adherence and thrombotic events, whether for cytoreductive therapy (ORR=1.25; 95% CI: 0.55–2.83) or for antithrombotic drugs (ORR=1.3; 95% CI: 0.45-3.72). This was also true for patients with PV (ORR=1.36; 95% CI: 0.65-2.82 and ORR=1.72; CI: 0.6-4.94, respectively) (*Online Supplementary Figure S2*).

Reasons for treatment non-adherence

To gain further insight into the causes of non-adherence to treatment, patients were asked to identify the most important reasons why they had skipped doses.

The two most frequent reasons were simply forgetfulness and difficulties in managing their treatment during holidays and travel (62% and 55%, respectively). Interestingly, the former was more frequently claimed by group 1 (48%) while the latter was the most frequent reason in group 2 (40%). In group 2, professional schedule constraints were also frequently brought up (26%). Some patients expressed more than one reason.

It is interesting to note that 12% of patients reported voluntarily omitting some treatment and that no patients mentioned side effects as a cause of non-adherence. All the reasons are presented in Figure 1.

It is also interesting that 20/55 (40.8%) of the patients who did not adhere fully to their treatment believed that forgetting their treatment on occasions had no influence on its efficacy, and only four of them increased the dose following a missed intake.

Incidence of thrombotic events and hematologic evolutions after completion of the questionnaire

To determine whether non-adherence to treatment had an impact on the evolution of the MPN, as has been

Table 2. Analyses of treatment non-adherence in the studied population.

	Whole cohort			Group 1			Group 2		
	Non-adherent pts	Adherent pts	*P*	Non-adherent pts	Adherent pts	*P*	Non-adherent pts	Adherent pts	*P*
Non-adherence (n/%)									
Cytoreductive drugs	65 (22.7)	221 (77.3)		55 (23.6)	178 (76.4)		10 (18.9)	43 (81.1)	
Antithrombotic drugs	46 (16.1)	240 (83.9)		33 (15.2)	200 (84.8)		13 (27.1)	40 (72.9)	
Both	26 (9.1)	260 (90.9)		21 (9)	212 (91)		5 (9.4)	48 (90.6)	
Total	85 (29.7)	201 (70.3)		67 (28.8)	166 (71.2)		18 (34)	35 (66)	
Age at the time of consultation (y)	68.1	70.7	0.007	66.6	73.4	*0.0013*	61.1	56.8	*0.31*
Sex ratio	1.1	0.66	0.07	0.96	0.65	*0.2*	2.33	0.72	*0.16*
Pathology (n/%)									
ET	32 (49.2)	118 (53.4)	0.55	27 (49.1)	101 (56.7)	*0.52*	5 (50)	17 (39.5)	*0.5*
PV	33 (50.8)	103 (46.6)		28 (50.9)	77 (43.3)		5 (50)	26 (60.5)	
Style of life (n/%)									
Living alone	25 (38.5)	64 (29)	0.15	23 (41.8)	53 (29.8)	*0.1*	2 (20)	11 (25.6)	*1*
City resident	33 (50.8)	121 (54.8)	0.12	28 (50.9)	100 (56.2)	*0.35*	5 (50)	21 (48.8)	*1*
History of thrombosis (n/%)	18 (27.7)	45 (20.4)	*0.21*	14 (25.5)	34 (19.2)	*0.31*	4 (40)	11 (25.6)	*0.4*
History of evolution (n/%)	7 (10.8)	30 (13.6)	*0.55*	4 (7.3)	24 (13.6)	*0.34*	3 (30)	6 (13.9)	*0.35*
Treatment (n/%)									
Hydroxycarbamide	41 (74.6)	121 (68.6)	*0.31*	41 (74.6)	121 (68.6)	*0.31*	na	na	
Doses (pills/wk)	12.3	10.1	*0.11*	12.3	10.1	*0.11*	na	na	
Duration (>1 y)	50 (90.9)	158 (89.3)	*0.73*	50 (90.9)	158 (89.3)	*0.73*	na	na	
Second-line therapy	21 (38.2)	67 (37.8)	*0.97*	21 (38.2)	67 (37.8)	*0.97*	na	na	
Pegylated interferon	42 (79.2)	10 (18.9)	*1*	na	na		42 (79.2)	10 (18.9)	*1*
Doses(injections/wk)	81.5 (53.1)	46.5 (26.1)	*0.05*	na	na		81.5 (53.1)	46.5 (26.1)	*0.05*
Duration (>1 y)	9 (90)	40 (93)	*1*	na	na		9 (90)	40 (93)	*1*
Second-line therapy	6 (60)	35 (81.4)	*0.2*	na	na		6 (60)	35 (81.4)	*0.2*
Drug diary	13 (24.1)	54 (30.5)	*0.36*	13 (24.1)	54 (30.5)	*0.36*	na	na	
Help to remember	9 (16.4)	19 (10.7)	*0.26*	9 (16.4)	19 (10.7)	*0.26*	na	na	
Same timing of intake	42 (64.6)	185 (83.7)	*0.0008*	38 (69.1)	157 (89.2)	*0.0003*	4 (40)	28 (65.1)	*0.17*
Own timing for intake	36 (55.4)	77 (34.8)	*0.003*	28 (52.8)	59 (33.7)	*0.03*	8 (80)	28 (66.6)	*0.84*
Other medications	44 (67.7)	175 (79.2)	*0.05*	39 (70.9)	146 (82.5)	*0.06*	5 (50)	29 (67.4)	*0.46*
Full blood counts at inclusion									
CHR (n/%)	33 (50.8)	144 (65.2)	0.03	28 (50.9)	110 (61.8)	*0.3*	5 (50)	34 (79.1)	*0.33*
Hemoglobin (g/dL)	13.6	13.3	0.21	12.4	12.1	*0.18*	13.9	13.5	*0.98*
Platelets (x10^9/L)	355	319	0.11	354	339	*0.51*	379	252	*0.08*
Leukocytes (x10^9/L)	6.15	6.4	0.26	7.81	7.12	*0.51*	5.7	5.7	*1*
Neutrophils (x10^9/L)	4	4.2	0.17	7.28	5.11	*0.45*	3.5	3.1	*0.74*

CHR: complete hematological response; ET: essential thrombocythemia; n: number; PV: polycythemia vera; pts: patients; wk: week; y: years; %: percent.

shown in other pathologies, the cohort was prospectively followed for an additional median time of 1.8 years (range, 1-2.4).

During the follow-up period, we recorded new events in 35/286 patients (12.2%), among whom 32/35 (91%) were in group 1. The recorded events were thrombosis in 18 cases (6.3%; 12 arterial, 6 venous), phenotypic evolution in 7 (2.4%; 1 case of post-ET PV, 3 cases of secondary myelofibrosis and 3 cases if secondary acute myeloid leukemias) and death in 17 cases (5.9%), all occurring in group 1 (P=0.05) (Table 3).

In the whole cohort, non-adherence to cytoreductive therapy was associated with a significant reduction in the complete hematologic remission rate compared to that in the group adhering to treatment: 50.8 *versus* 65.2% (P=0.03) (ORR=1.85, 95% CI: 1.01-3.36). This difference was lost when analyzing groups 1 and 2 separately (Table 2).

No significant association was found between non-adherence and thrombosis or death. In group 2, non-adherence was not significantly associated with the outcome, but there were only a few events in this group. However, non-adherence to cytoreductive therapy was associated with an increased risk of hematologic transformation both in the whole cohort [4/65 (6.1%) versus 3/221 (1.3%), P=0.05; ORR=4.73, 95% CI: 0.78-33.14] and in group 1 [4/55 (7.3%) *versus* 3/178 (1.8%), P=0.05; ORR=4.54, 95% CI: 1-31.98]. Furthermore, these evolutions also occurred sooner in the treatment non-adherent group (P=0.05) (Figure 2).

Discussion

The importance of treatment compliance has now been clearly established in many pathological conditions, and especially in hematologic malignancies.[9,13-16] These studies typically demonstrate that poor adherence has a negative impact on clinical evolution. However, to the best of our knowledge, no such data were previously available regarding patients with Philadelphia-negative MPN. Yet, these chronic disorders have very variable clinical evolution and are prone to complications. We, therefore, decided to assess MPN patients' compliance with cytoreductive and antithrombotic treatments.

Many ways of assessing patients' adherence to treatment have been described, including pill counts, drug plasma levels, various microelectronic monitoring systems and dispensation by a third party. All methods have their pros and cons. We chose to assess patients' adherence using a single questionnaire. The self-evaluation method using a questionnaire is easier and less expensive to implement, even though patients' reluctance to admit omitting drug intake could theoretically bias the results. Because of the blind process of this study, there was no influence from the consultant or staff on completion of the questionnaires. We cannot, however, exclude some degree of under-declaration of non-adherence. Despite this fact, the proportion of patients not adherent with treatment in this study was equivalent to that reported by Marin *et al.* who used a microelectronic monitoring system, suggesting that the questionnaire does not grossly underestimate non-

Table 3. New events observed after completion of the questionnaires.

		Non-adherent patients	Adherent patients	P
Whole cohort				
N. of patients	286	65	221	
Events (n/%)				
Total	35 (12.2)	8 (12.3)	27 (12.2)	0.98
Thrombosis	18 (6.3)	4 (6.1)	14 (6.3)	1
Evolution	7 (2.4)	4 (6.1)	3 (1.4)	0.05
Death	17 (5.9)	2 (3.1)	15 (6.8)	0.37
Group 1				
N. of patients	233	55	178	
Events (n/%)				
Total	32 (13.7)	7 (12.7)	25 (14)	0.8
Thrombosis	16 (6.9)	3 (5.6)	13 (7.3)	0.77
Evolution	7 (3)	4 (7.3)	3 (1.8)	0.05
Death	17 (7.3)	2 (3.7)	15 (8.4)	0.37
Group 2				
N. of patients	53	10	43	
Events (n/%)				
Total	3 (5.7)	1 (10)	2 (4.7)	0.47
Thrombosis	2 (3.8)	1 (10)	1 (2.3)	0.34
Evolution	0	0	0	na
Death	0	0	0	na

na: non-applicable; n: number; pts: patients; %: percent.

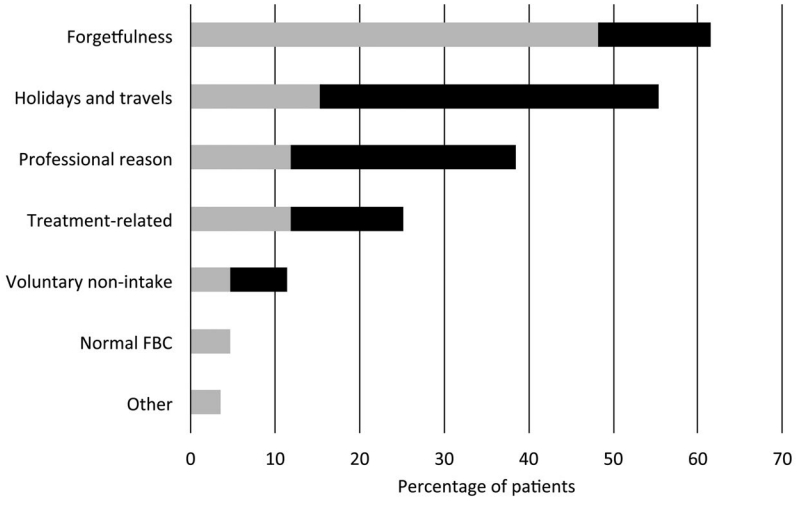

Figure 1. Reasons for non-adherence. Gray represents the answers of patients from group 1 (oral intake) and black represents the answers of patients from group 2 (sub-cutaneous injection). The results are expressed as percentage of answers. Patients could state more than one reason for non-adherence. FBC: full blood count.

adherence. This study by Marin *et al.* in patients with chronic myeloid leukemia found that 26% of patients were non-adherent with their treatment, while in the present study, 22% were non-adherent to cytoreduction and 29% to either cytoreduction or antithrombotic drugs. Furthermore, our questionnaire provided insight into the reasons why the patients missed taking their drugs.

The causes for non-adherence were also approached in chronic myeloid leukemia by Marin *et al.* who reported younger age as a major factor.[6] Likewise, in acute lymphoblastic leukemia, Bhatia *et al.* found that adherence to maintenance therapy was suboptimal in teenagers among whom the non-adherence rate was 20.5%.[9] This study also pointed to socio-economic conditions as a major determinant of adherence. In our study, factors significantly associated with non-adherence were found mostly in patients who took their treatment orally, and included younger age, choosing the pill intake schedule themselves, dispersing their intake through the day and a small number of different drugs to take (Table 2). This indicates that, in addition to personal traits (age, ethnic, socio-economic background), the way of managing patients' drug intake (route of administration, time of the day, number of different treatments) has an impact on adherence. Interestingly, patients receiving subcutaneously injected cytoreduction showed poorer adherence to oral antithrombotic drugs than patients receiving oral cytoreduction. Together with the fact that treatment adherent patients were more likely to be taking several drugs and the fact that diabetic patients showed a higher rate of adherence to treatment, this suggests that having a higher number of oral drugs to take makes it less likely to miss one intake. Physicians should therefore probably put even more effort into helping patients being treated with subcutaneous cytoreduction ensure good adherence to their antithrombotic drug treatment. Unexpectedly, the occurrence of adverse effects to the drugs was not reported by patients as a determining factor in their non-adherence. We also observed that having suffered a complication and/or phenotypic evolution of the disease did not increase adherence to treatment. This is coherent with the fact that most non-adherent patients reported not believing that non-adherence may affect the clinical outcome of their disease. These elements suggest that good comprehension of the disease and treatment should improve adherence, as has been shown in other chronic diseases such as diabetes.

To assess the risk of transformation associated with non-adherence, we analyzed the events (thrombosis, phenotypic evolution) that occurred before compilation of the questionnaire (retrospective study) and followed up the cohort prospectively. The frequencies of events before compilation of the questionnaire (median time of observation of 11.7 years) were similar in treatment adherent and non-adherent patients. Thrombotic events occurred in 19.2% of treatment adherent and 25.5% of treatment non-adherent patients. These frequencies are slightly higher than those reported for patients with PV (26.4% *versus* 9.3-19%) and in accordance with the scientific literature for patients with ET (18.2% *versus* 7.6-22%).[17]

Regarding the events that occurred during the prospective follow-up, the median time was shorter (1.8 years). However, events were recorded in 35 (12.2%) patients. No differences were noted between the treatment adherent and non-adherent groups regarding thrombotic events or death, but phenotypic evolution was more frequent in the treatment non-adherent patients, especially in group 1. Although this result must be interpreted with caution given the small number of affected patients (n=7), the impact of adherence on phenotypic evolution of MPN is reminiscent of data reported for chronic myeloid leukemia or acute lymphoblastic leukemia, confirming the importance of constant therapeutic pressure for the control of malignant clones. Unexpectedly, the impact on thrombosis was less obvious. This may be related to the fact that thrombosis is a more acute event, depending on the immediate hemostatic status at the time of thrombus constitution, whereas the phenotypic evolution of chronic hematologic malignancies may be more the result of long-term evolution of the clone, reflecting its exposure to therapeutic pressure. This is coherent with the observation that treatment non-adherent patients were less likely to achieve a complete hematologic response. Only a few events were observed in group 2, suggesting that interferon may ensure better long-term control of MPN clones as has been suggested in recent publications.[18] Further evaluation of the long-term impact of non-adher-

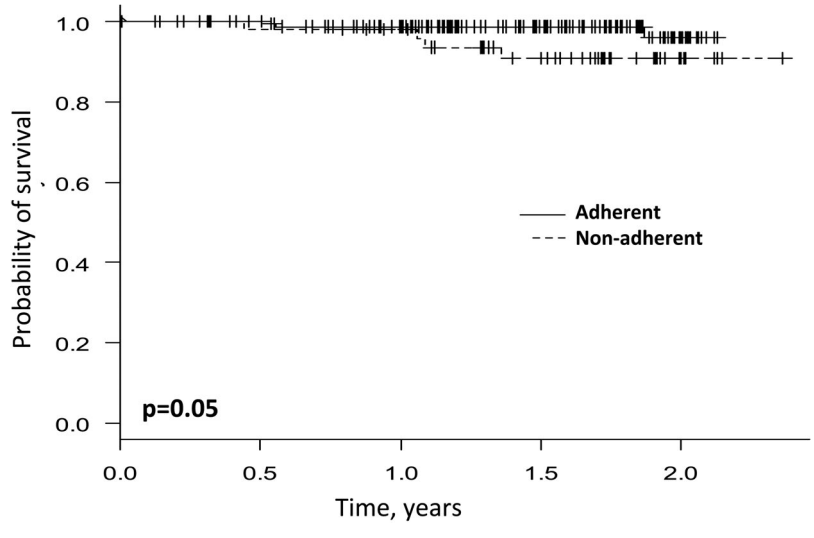

Figure 2. Kaplan-Meier evolution-free survival curves for treatment adherent or non-adherent patients.

ence would be necessary to confirm these observations. This evaluation will be not possible with our cohort, since after the blinding had been removed, all treatment non-adherent patients were managed to improve their adherence. Larger multicenter studies could confirm the "non-adherent profile" which sometimes pointed to unexpected findings, such as taller height in male patients not adhering fully with treatment.

To our knowledge, OUEST is the first study on the incidence, determinants and impact of treatment non-adherence on the outcome of patients with Philadelphia negative MPN. The occurrence of non-adherence is relatively common, with an incidence of 28%, but is generally moderate. Younger age and the route and schedule of drug administration seem to be the major determinants of poor treatment adherence. Phenotypic evolution seems to be more frequent in the group not adherent to treatment, suggesting that cytoreductive drug pressure could help to reduce the risk of evolution. Major efforts should be invested into improving treatment adherence.

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