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### **► To cite this version:**

Margaux Wiber, Elsa Maitre, Jean-Marc Poncet, Virginie Duchenet, Gandhi Damaj, et al.. A population-based study of hairy cell leukemia over a period of 20 years. *Cancer Treatment and Research Communications*, 2020, 25, pp.100236 -. <10.1016/j.ctarc.2020.100236>. <hal-03493187>

**HAL Id: hal-03493187**

**<https://hal.science/hal-03493187v1>**

Submitted on 21 Nov 2022

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# A population-based study of hairy cell leukemia over a period of 20 years

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**Keywords.** Hairy cell leukemia, HCL, epidemiology

## **Abstract**

There are limited population-based studies of hairy cell leukemia (HCL), a rare chronic lymphoproliferative disorder of B-cells. We conducted a population-based study that included all patients diagnosed with HCL between 1996 and 2016 in Western Normandy. Recorded data focused on medical history, clinical presentation, biological results, treatment modalities in the first line and in relapsed/refractory patients and the occurrence of secondary malignancies.

One hundred and twenty-three HCL patients were registered in the database. HCL represented 0.7% of all malignant hematological disorders and 3.0% of all leukemia. The overall age-standardized incidence ratio (SIR) was 0.39/100,000 inhabitants in men and 0.09/100,000 in women, and it remained stable over the 20-year period analyzed. One hundred and seven patients (88%) received first-line treatment, 33 patients (27%) received at least 2 lines of treatment and 14 patients (11%) received more than 2 lines. Cladribine used as first-line treatment induced a high hematological complete response (HCR) rate of 92%. The median overall survival (OS) was over 15 years, with 5-year and 10-year survival rates of 84% and 70.5%. No significant differences in OS were observed between men and women, between the calendar periods studied or between patients who received a single line treatment with IFN- $\alpha$  or PNA. The risk of relapse was higher with IFN- $\alpha$  treatment, requiring subsequent treatments in that patients. The time to next treatment (TTN) tends to be longer for PNAs compared to IFN- $\alpha$  even if difference is not significant. Secondary cancers were observed in 9/123 patients (7.3%) with solid tumors in 8 patients and hematological malignancy in one patient.

Our data confirm in real life that single courses of cladribine administered to patients with HCL induce high response rates, the majority of which are HCR. Relapses seem less frequent than with IFN- $\alpha$  and the administration schedule is less restrictive for the patients. The emergence of chemo-immunotherapy and the development of effective new drugs such as recombinant immunotoxins and BRAF targeting will offer new possibilities in the management of HCL patients.

## Introduction

Hairy cell leukemia (HCL) is a rare and indolent B-cell chronic lymphoproliferative disorder that accounts for 2% of all leukemia. HCL is four to five times more frequent in men than women. At diagnosis, the median age of HCL patients is 55 years old. Patients with HCL commonly present with splenomegaly, infections, or pancytopenia. Abnormal hairy cells are characterized by the expression of CD103, CD123, CD25 and CD11c antigens, in addition to the pan-B-cell antigens CD19, CD20 or CD22 [1]. In more than 80-90% of cases, the *BRAF*<sup>V600E</sup> mutation can be identified [2]. Over the past few decades, HCL treatment has progressively changed over time. In the 1980s, splenectomy was the standard treatment. Interferon alpha (IFN- $\alpha$ ) was subsequently introduced and used until the early 2000s [3]. Then the purine nucleoside analogues (PNAs) pentostatin (2'-deoxycoformycin) [4] and cladribine (2-chlorodeoxyadenosine) [5] were introduced; these drugs are currently the first-line therapeutic option for symptomatic HCL patients [6]. New drugs have recently emerged, especially BRAF inhibitors (BRAFi) (vemurafenib, dabrafenib), BRAFi associated with MEK inhibitors (trametinib, cobimetinib), CD22-targeted therapy and BCR inhibitors (BCRi) (ibrutinib). In all HCL cases, long-term follow-up is mandatory because of the risk of relapses and secondary malignancies.

The few available population-based studies of HCL are limited in scale [7–13]. We analyzed the clinical and biological data of 123 new HCL cases recorded between 1996 and 2016 in the Regional Register of Hematological Malignancies of Western Normandy (RRHMNO). The main objectives of the study were to describe in the real life the clinical and biological characteristics of HCL patients; to establish the crude incidence rate and the overall age-standardized incidence ratio (SIR); to analyze the overall survival (OS), the time to next treatment (TNT), and also the risk of secondary malignancies.

## Patients and methods

**Patients.** The RRHMNO is a regional specialized registry in hematology, which actively records all incident cases of hematological malignant diseases (HM), including all HCL patients living in Western Normandy. Western Normandy is composed of three departments, called La Manche, l'Orne and Le Calvados. The RRHMNO covers a population of 1,477,349 inhabitants, 693,679 inhabitants in Le

Calvados, 498,362 inhabitants in La Manche and 285 308 inhabitants in l'Orne (INSEE estimates, January 2016). The RRHMNO belongs to the network France Cancer Incidence and Mortality (Francim), composed of general and specialized registers allowing the surveillance of approximately 8 million people corresponding to 13 to 14% of the French population. The WHO classification of tumours of the haematopoietic and lymphoid tissues (4<sup>th</sup> edition) was used to classify the hematologic malignancies. Validated cases were registered in a database hosted on a secure server of the hospital of Caen, France. Recorded data focused on medical history, clinical presentation, biological results, treatment, and secondary neoplasms.

**HCL diagnosis.** We selected all HCL patients diagnosed between 1996 and 2016, with a follow-up by the national directory for the identification of natural persons (RNIPP) for vital statistics until September 15, 2018. Patients with the variant form of hairy cell leukemia (HCL-v) were excluded. HCL diagnosis was based on identification of hairy cells in the peripheral blood and/or bone marrow. In most cases, flow cytometry (FCM) was achieved in the peripheral blood and/or bone marrow. In addition, the identification of the *BRAF*<sup>V600E</sup> mutation was performed in the most recent cases. Symptomatic HCL was defined as a hemoglobin level less than 110 g/L, platelet count less than 100x10<sup>9</sup>/L or neutrophil count less than 1x10<sup>9</sup>/L. These are the limit values that determine the implementation of a drug treatment according to the recommendations [14]. Secondary malignancies were defined as second neoplasms diagnosed after HCL diagnosis.

**Assessment of response.** The definition of complete response (CR) required normalization of peripheral blood counts: hemoglobin > 11 g/dL without transfusion, platelets > 100,000/μL and an absolute neutrophil count >1500/μL with absence of morphologic evidence of HCL on both the peripheral blood smear and the bone marrow examination [17]. In addition, patients were required to lack any palpable splenomegaly on physical examination and to have achieved full resolution of all symptoms related to the disease. The vast majority of our patients did not have a follow-up bone marrow examination, which is not mandatory outside of clinical trials according to French recommendations [15]. In our study, we defined hematological complete response (HCR) as recovery of blood counts and resolution of all clinical symptoms.

**Statistical analysis.** Categorical variables were summarized with frequencies and percentages and compared using Fisher's exact test or the  $\chi^2$  test, depending on their distribution. Continuous variables were summarized with a median value and range and compared using the Mann-Whitney U test or the Kruskal-Wallis test. OS was defined as the time from the date of HCL diagnosis until death from any cause or the date of last observation. Time to next treatment (TNT) was defined as the time from start date of first-line treatment until start date of second-line treatment, death from any cause or date of last observation. OS and TNT were plotted using the Kaplan-Meier method and compared by a log-rank test. Univariate analysis was performed using the following variables: sex, diagnosis period and first-line therapy. Multivariable analysis was not performed due to the low number of events. *P*-values were considered to indicate statistical significance when  $<0.05$ . All statistical analyses were performed using GraphPad Prism version 8.0.2 for Windows (GraphPad Software, La Jolla California USA, [www.graphpad.com](http://www.graphpad.com)).

Concerning the description of the RRHMNO general data, the SIR of most hematological malignancies in Western Normandy was assessed between 1997 and 2016. For the reference population, we chose the median year of the period analyzed, 2007. The annual gross rate was calculated by dividing the headcount by the population of Lower Normandy in 2007 and was reported as the number per 100,000 inhabitants. The SIR was calculated by multiplying the annual gross age-class rate by the 2007 world population for each age group. Then, the different standardized rates were added together and divided by the 2007 global population.

## Results

**Distribution of malignant hematological disorders.** Over the period 1996-2016, RRHMNO recorded 18.324 hematological malignancies, 9.898 cases (54%) in men and 8.426 (46%) in women. The crude incidence rate and the overall SIR for each malignant hematologic disorder are listed in Table 1. In men, the top three malignant hematologic disorders were myelodysplastic syndromes (1.446 patients), chronic lymphocytic leukemia (1.274 patients) and multiple myeloma/plasmacytoma (1.133 patients). In women, myelodysplastic syndromes (1,233 patients), myeloproliferative neoplasms (1.157 patients) and multiple myeloma/plasmacytoma (1.051 patients) were identified in the database.

**Study population characteristics.** One hundred and twenty-three patients, 102 men (82.9%) with a median age at diagnosis of 63 years (33-92) and 21 women (17.1%) with a median age at diagnosis of 59 years (36-97), were included in the study. Only 2 patients (1.6%) were between 30 and 39 years old, 76 patients (61.8%) were between 40 and 69 years old, and 45 patients (36.6%) were  $\geq$  70 years old. Patient characteristics are presented in Table 2. At diagnosis, 41 patients (33%) had splenomegaly, and 24 patients (19.5%) had infections, mostly lung infections (50%). One patient presented atypical mycobacterial infection and two patients had lymph node tuberculosis. Eight patients (6.5%) had hemorrhagic manifestations. Almost all patients had at least one cytopenia with, in order of frequency, thrombocytopenia in 76 patients (62%), neutropenia in 66 patients (54%) and anemia in 47 patients (38%). Pancytopenia was observed in 25 patients (20.3%) (Table 2). Bone marrow aspiration showed medullary infiltration by hairy cells, associated with a decrease in marrow cells in 79.3% of cases. Bone marrow biopsy was performed in only 18.7% of cases. FCM was performed in 84/123 patients (68.3%), and the clonal nature of the cells by the isotypic restriction of the immunoglobulin light chains was confirmed in all cases. The expression of CD103, CD25, CD11c and CD123 markers was positive in 95% of cases (40/42 patients). The expression of only 3 of the 4 markers was observed in two patients: negative markers were either CD103 or CD123. The *BRAF*<sup>V600E</sup> mutation was demonstrated in all 40 recently tested patients.

**Standardized incidence ratio (SIR).** HCL represented 0.7% of all malignant hematological disorders and 3.0% of all leukemia, 1.0% and 4.5% in men and 0.3% and 1.2% in women, respectively. The crude incidence rate was 0.71/100,000 in men and 0.15/100,000 in women. The overall SIR was 0.39/100,000 inhabitants in men and 0.09/100,000 inhabitants in women (Table 1).

**Overall Survival (OS)** The median OS was over 15 years (188 months), with a 5-year and 10-year survival rate of 84% and 70.5%, respectively (Figure 1). The characteristics and treatments were similar between men and women, and no significant difference in OS was observed (*P*-value=0.11).

**Treatment.** After a median follow-up of 60 months (0-264), 74 patients (60.2%) were alive, and 49 (39.8%) patients died. The median number of lines of treatment was 1.3 (0-5). Sixteen patients (13%) did not receive treatment. Out of the 16 patients without treatment, 5 symptomatic HCL patients died very shortly after diagnosis, 4 patients

were over 75 years old and presented comorbidities, 6 patients were asymptomatic, and one patient declined the treatment. One hundred seven patients (88%) received first-line treatment, 33 patients (27%) at least 2 treatment lines and 10 patients (8%) received more than 2 lines. As first-line treatment, 47 patients received IFN- $\alpha$  (43.9%), 49 patients (45.8%) received cladribine and 11 patients (10.3%) received pentostatin. Hematological complete response (HCR) was observed in 97.5%, 92% and 90% of cases, respectively. Cladribine and pentostatin were combined in the same group we called PNAs for statistical analyses. Patient characteristics (age, sex ratio, clinical presentation, and blood count) according to first-line treatment were similar with the exception of the infection rate, which was higher in PNAs group ( $P$ -value=0.0008) (Tableau 3). The follow-up period was also statistically different with a median follow-up of 183 months (range, 0.01-264) in IFN- $\alpha$  group and only 87 months (range, 1-231) in PNAs group ( $P$ -value <0.0001). Time to next treatment (TNT) was compared according to first-line treatment. The median TNT was 147 months for PNAs and 84 months for IFN- $\alpha$ . However, the difference was not statistically significant ( $P$ -value=0.1481) (Figure 2). Overall survival (OS) was compared between patients, who received just only one line of treatment, either IFN- $\alpha$  or PNAs. The difference was not statistically significant between both groups, with a median OS of 153 months for patients treated with IFN- $\alpha$  and not reached for PNAs ( $P$ -value=0,4763). However, a second-line treatment was required more often in patients treated in first line by IFN- $\alpha$  (20/47, 43%) compared to those treated by PNAs (13/60, 22%) ( $P$ -value=0,03408). Of the 20 patients who received IFN- $\alpha$  as first-line, 14 received PNAs as second line, 5 IFN- $\alpha$  and one patient was splenectomized. Of the 13 patients who received PNAs as first-line, 7 received PNAs again, of the same type as in first line in 5 out of 7 cases, 3 received rituximab, 2 received IFN- $\alpha$  and one received the combination of pentostatin plus rituximab. The mean number of treatment lines was 1.6 (range, 1-5) in the IFN- $\alpha$  group and 1.3 (range, 1-3) in the PNAs ( $P$ -value=0.0095).

The study was divided into 4 calendar periods: 1996-1999, 2000-2004, 2005-2009 and 2010-2016. The number of new HCL cases yearly remained stable over time, with a mean of 6 cases per year (3-13). The characteristics of the patients were also similar and did not change with time, with the exception of a smaller percentage of women over the period from 2005 to 2009 (sex ratio: 11.0). Regarding the

management of HCL patients, IFN- $\alpha$  was gradually replaced by cladribine in first line. Some patients who received IFN- $\alpha$  in the first line, benefited from the introduction of PNAs as second line (n=14). The percentage of patients treated with pentostatin remained similar over time. Rituximab emerged in the therapeutic arsenal mainly from 2010, and was used in second line and more, either in monotherapy (n=6) or combination (n=2). In the univariate analysis, we did not observe a statistically significant difference in OS between the different periods analyzed (Figure 3).

**Secondary malignancies.** Nine (7.3%) secondary malignancies were diagnosed after HCL diagnosis. Eight patients developed solid tumors, and 1 developed hematological malignancy. The solid tumors comprised prostate cancers (n=4), lung cancers (n=2), a skin and facial tumor, and a pancreatic cancer. The hematological malignancy was an EBV-induced large B-cell lymphoma. The median time from HCL diagnosis to secondary malignancy was 76 (range, 12-258) months for solid tumors. The time from HCL diagnosis to the large B-cell lymphoma was 184 months. Furthermore, 4 malignancies were diagnosed concurrently with HCL: renal cell carcinoma, colorectal cancer, chronic lymphocytic leukemia, and follicular lymphoma.

## Discussion

HCL is a rare hematologic disorder, and few population-based studies have been published [7–13]. This study represents in real life the experience of HCL management in a single French center (Western Normandy) over a period of 20 years. HCL diagnosis was established, including clinical, biological, and molecular studies. The demographic characteristics are similar to those reported in the literature [7–13,16]. Note that only one-third of patients presented splenomegaly, while most studies reported a rate of approximately two-thirds. We can explain the difference by an earlier diagnosis. Three patients presented mycobacterial infections, in line with the known particular susceptibility to this type of infections. The immunologic panel we used, included initially CD103 and has widened over time with other typical markers, CD25, CD11c and CD123. These markers are usually negative in other HCL-like disorders: HCL-v, splenic marginal zone lymphoma (SMZL) and splenic diffuse red pulp small B-cell lymphoma (SDRPL). In the current study, we found an immunological score greater than or equal to 3 in all cases. The *BRAF*<sup>V600E</sup> somatic mutation was initially described in 2011 [2] and is now considered the molecular

hallmark of the disease. The absence of the *BRAF* gene mutation was reported in up to 10% to 20% of patients with HCL and could constitute a subgroup of HCL patients with *IGHV4-34* rearrangement and a poor prognosis [17,18]. In particular, the *BRAF<sup>V600E</sup>* mutation must be searched for in cases of relapsed/refractory disease to rule out the diagnosis of HCL-v. Moreover, the presence of the mutation is necessary for the use of BRAFi. In our cohort, all 40 tested samples presented the *BRAF<sup>V600E</sup>* mutation.

The therapeutic management of the patients is in line with the main recommendations: PNAs remain the gold standard of HCL in first line treatment. The second line treatment is based on immunochemotherapy associating PNAs plus rituximab. The new drugs (BRAFi, BCRI, immunotoxins) [6] introduced more recently are an option in cases of relapsed/refractory HCL: they were not still used in our cohort, with HCL diagnosis between 1996 and 2016.

The incidence of HCL remained stable over the period analyzed, with similar patient characteristics. We did not observe an improvement of the OS over time. Recent data [8] showed an improvement in the relative survival (RS) of patients only aged between 60 and 69 years and analyzed between 2001-2015, as compared to 1989-1993. However, the RS was similar between 1994-2000 and 2001-2015.

We found no statistically significant difference in OS between men and women. The median age at diagnosis was 59 years in women and 63 years in men. A recent Israeli study reported better outcomes in females than in males [19]. A similar difference was also observed in patients with chronic lymphocytic leukemia (CLL), with women generally having an earlier disease stage at diagnosis and fewer comorbidities [20]. In non-Hodgkin lymphomas, women have a better prognosis than men due to a better response to immunochemotherapy [21]. In HCL, the life expectancy of patients being close to that of the general population [8], the better survival of women might simply reflect their better general longevity. In our study, we did not show statistically significant difference in OS between patients who received only one line of treatment by either IFN- $\alpha$  or PNA. This may be explained by the small number of patients in our cohort and by the difference of the follow-up time. It is important to note that OS is not probably a relevant indicator in a disease with a good long-term survival.

Most patients who received first-line PNA treatment did not need a second line compared to those treated with IFN- $\alpha$ . Moreover, the time to next treatment, even if it is not statistically demonstrated, seems to be longer in PNAs group (median TNT: 147 months) than in the IFN- $\alpha$  group (median TNT: 87 months), which suggests a longer duration of response to treatment. In addition, the modalities of taking cladribine over 5 consecutive days are less restrictive for the patient than those of IFN- $\alpha$ , which is administered subcutaneously three times weekly and produces frequent side effects. Indications for IFN- $\alpha$  are now more restricted in patients with severe febrile neutropenia ( $<0.2$  G/L), active infection and in pregnant women [6,14].

The rate of secondary malignancies reported in our study was 7.3% is rather in the lower range of what we find in the literature (range, 4-24%) [7,9,10,22–34]. The differences in the incidence of secondary malignancies could depend on the type of cancer reported, the number of patients in the cohort and, importantly, the length of patient follow-up. Data in the literature are controversial concerning the link between HCL and the impact of the treatment and the increased risk of secondary malignancies. We showed in 2014 [35] an increased risk of secondary neoplasm, with SIR = 1.86 (95% CI, 1.34-2.51), independent of the type of treatment. Secondary malignancies would thus be linked to the pathology itself and probably to the intrinsic immune alterations induced by HCL that diminished antitumor defense [36–39]. If several types of cancers can occur, some studies report a particularly increased risk of developing non-Hodgkin B-cell lymphomas [10,34,35] and skin tumors [34,40,41]. In our study, we observed different types of tumors, including one skin tumor and 1 lymphoid disorder. The SIR could not be calculated for our cohort due to the low number of events.

In conclusion, we report data from the first French registry study spanning an extended period of 20 years. The demographic characteristics of the HCL cohort are similar to what is usually described in the literature, including the frequency of secondary malignancies. The need of a long-term follow-up is mandatory in HCL patients. We did not find any difference in OS over time or in terms of first-line treatment. The number of patients in our cohort is probably a limiting factor. PNAs, with or without the addition of rituximab, are now recommended in first line treatment; this approach will decrease the relapse rate. The new drugs may also be effective in

relapsed/refractory patients and change the management of patients with relapsed/refractory HCL.

**Funding statement:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Incidence of hematological malignancies in Western Normandy (1996-2016).

	Men (N) Western Normandy 1996-2016	Crude incidence rate/100,000	Standardized incidence rate (SIR) /100,000	Women (N) Western Normandy 1996-2016	Crude incidence rate/100,000	Standardized incidence rate (SIR) /100,000
Acute leukemia	838	5.92	4.24	801	5.31	3.67
Myeloproliferative disorder	1120	7.91	4.31	1157	7.67	4.01
Myelodysplastic syndrome	1446	10.22	4.10	1233	8.18	3.04
Chronic myelomonocytic leukemia	182	1.29	0.51	119	0.79	0.30
B-cell lymphoma including :	2444	17.27	9.24	2111	14.00	7.01
Diffuse large B-cell lymphoma	1014	7.17	3.94	931	6.17	3.07
Follicular lymphoma	473	3.34	1.97	468	3.10	1.73
Marginal zone lymphoma	342	2.42	1.20	303	2.01	0.98
Mantle cell lymphoma	232	1.64	0.73	102	0.68	0.29
Other B-cell lymphomas	383	2.71	1.41	307	2.04	0.94
Mature B-cell lymphoproliferative disorder including:	1704	12.04	5.72	1155	7.66	3.43
Chronic lymphocytic leukemia	1274	9.00	4.29	943	6.25	2.81
Waldenstrom macroglobulinemia	321	2.27	1.01	182	1.21	0.51
<b>Hairy cell leukemia</b>	<b>102</b>	<b>0.71</b>	<b>0.39</b>	<b>21</b>	<b>0.15</b>	<b>0.09</b>
Prolymphocytic leukemia	9	0.06	0.03	8	0.05	0.02
Myeloma and plasmacytoma	1133	8.01	3.85	1051	6.97	3.18
Hodgkin lymphoma	443	3.13	2.96	345	2.29	2.44
T-cell lymphoma	388	2.74	1.73	270	1.79	1.20
Mature T-cell lymphoproliferative disorder	107	0.76	0.40	106	0.70	0.36
Other lymphomas	72	0.51	0.25	58	0.38	0.14
Histiocytosis	21	0.15	0.15	20	0.13	0.18
<b>TOTAL</b>	<b>9898</b>	<b>69.95</b>	<b>37.45</b>	<b>8426</b>	<b>55.88</b>	<b>28.96</b>

Table 2. Patient characteristics ( $n=123$ ).

	<b>n=123</b>
Median age at diagnosis, years (range)	62.0 (33.0-97.0)
Male:female ratio	4.9
Follow-up (months), median (range)	60 (0-264)
Adenopathies, $n$ (%)	4 (3.3)
Splenomegaly, $n$ (%)	41 (33.3)
Alteration of the general state, $n$ (%)	29 (23.6)
Hemorrhagic manifestations, $n$ (%)	8 (6.5)
Infections, $n$ (%)	24 (19.5)
Neutrophil count ( $\times 10^9/L$ ), median (range)	0.92 (0.00-4.40)
Lymphocytes count ( $\times 10^9/L$ ), median (range)	1.30 (0.20-9.13)
Monocytes count ( $\times 10^9/L$ ), median (range)	0.03 (0.00-1.00)
Hemoglobin (g/L), median (range)	120 (44-155)
Platelet count ( $\times 10^9/L$ ), median (range)	86 (17-494)
Neutropenia (neutrophil count $< 1 \times 10^9/L$ ), $n$ (%)	66 (53.7)
Anemia (hemoglobin $< 110$ g/L), $n$ (%)	47 (38.2)
Thrombopenia (platelet count $< 100 \times 10^9/L$ ), $n$ (%)	76 (61.8)
Pancytopenia, $n$ (%)	25 (20.3)

Table 3. Comparison of patient characteristics according to first-line treatment.

	Purin analogs (n=60)	Interferon (n=47)	<i>P</i> -value
Median age at diagnosis, years (range)	60 (33-89)	65 (41-84)	0.0997
Male:female ratio	6,5	4,2	0.4369
Follow-up (months), median (range)	87 (1-231)	183 (0-264)	<b>&lt;0,0001</b>
Splenomegaly, <i>n</i> (%)	23 (38%)	15 (32%)	0.5453
Alteration of the general state, <i>n</i> (%)	17 (28%)	9 (19%)	0.3644
Infections, <i>n</i> (%)	18 (30%)	2 (9%)	<b>0.0008</b>
Neutrophil count (x10 <sup>9</sup> /L), median (range)	0.78 (0.18-4.40)	1.00 (0.16-2.02)	0.2962
Hemoglobin (g/L), median (range)	12.1 (4.9-15.5)	11.4 (4.4-15.2)	0.0921
Platelet count (x10 <sup>9</sup> /L), median (range)	83 (17-320)	87 (21-494)	0.6625

Figure 1. Overall survival (OS) for all patients (n=123).

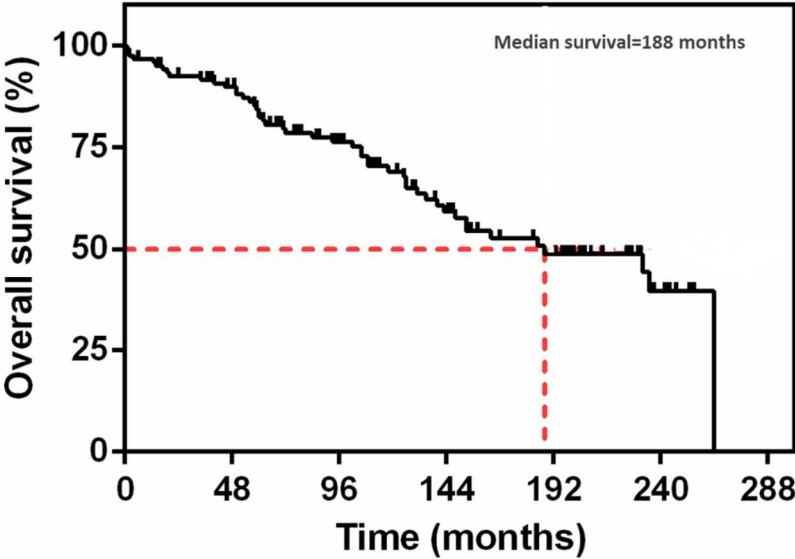


Figure 2. Time to next treatment (TNT) according to first-line therapy.

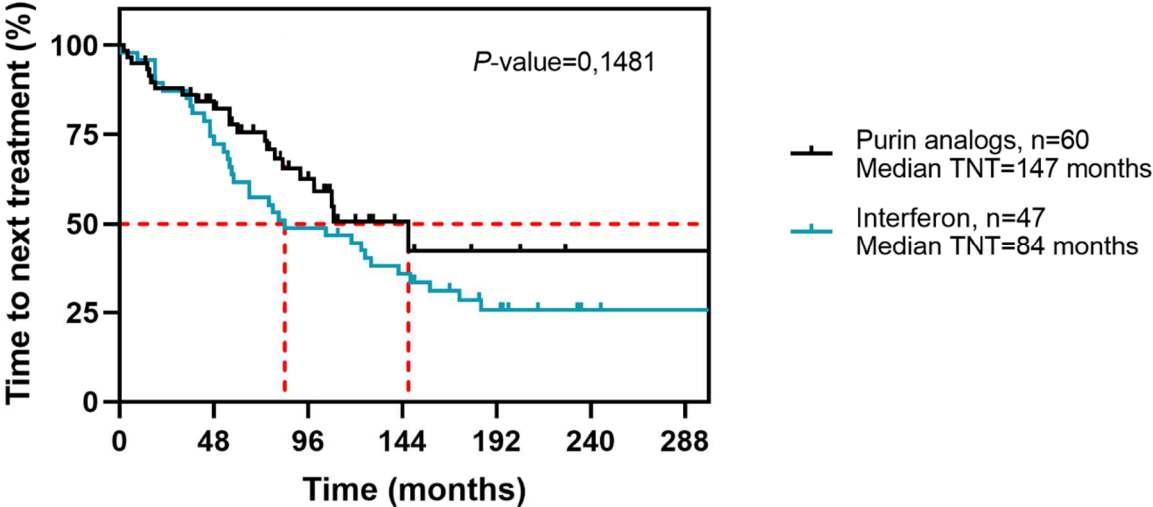
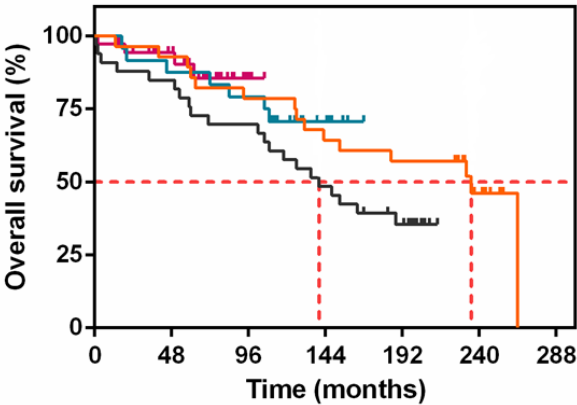


Figure 3. Overall survival (OS) according to the period of diagnosis.



P-value	1996-1999	2000-2004	2005-2009
2000-2004	0,0853		0,1412
2005-2009	0,8980	0,1412	
2010-2016	0,7052	0,1283	0,6724

- 1996-1999; Median survival=235 months (n=29)
- 2000-2004; Median survival=140 months (n=33)
- 2005-2009; Median survival=not reached (n=24)
- 2010-2016; Median survival=not reached (n=37)