Annals of Hematology (2019) 98:2367–2377
https://doi.org/10.1007/s00277-019-03778-9

ORIGINAL ARTICLE

Characteristics, combinations, treatments, and survival of second primary hematological neoplasm: a retrospective single-center cohort of 49 patients (*Hemo*^{2} *study*)

Thomas Chalopin[1] · Nicolas Vallet[1] · Flavie Arbion[2] · Carole Barin[3] · Emmanuelle Rault[4] · Alban Villate[1] · Martin Eloit[1] · Laurianne Drieu La Rochelle[1] · Amélie Foucault[4] · Marjan Ertault[1] · Caroline Dartigeas[1] · Lotfi Benboubker[1] · Marie-Hélène Estienne[4] · Jorge Domenech[4,5] · Olivier Hérault[4,5] · Emmanuel Gyan[1,5,6]

Received: 15 February 2019 / Accepted: 5 August 2019 / Published online: 27 August 2019

Abstract

The coexistence of dual hematological neoplasms is very rare. Sequential or synchronous neoplasms in hematology are an uncommon and complex clinical situation. The aim of the *Hemo*^{2} study was to describe the clinical characteristics and analyze the outcome of these patients. We performed a retrospective review of all patients diagnosed with sequential or synchronous hematological malignancies in the university hospital of Tours, between 2007 and 2018. We identified 49 patients in our study, with a prevalence of 0.89%. Sequential and synchronous combinations were found in 36 (73%) and 13 (27%) patients, respectively. One patient presented three sequential neoplasms. The median cumulative incidence was 6 years (95% CI 3–7). Among all neoplasms diagnosed ($n = 99$), we found 79 lymphoid neoplasms (LNs) (80%) and 20 myeloid neoplasms (MNs) (20%). Sex ratio was 1.88 with 65% of males and 35% of females. The most common LNs were Hodgkin lymphoma ($n = 16$; 16%) and multiple myeloma ($n = 11$; 11%). The most frequent MN was essential thrombocythemia ($n = 5$; 5%). The most common combination was Hodgkin lymphoma and follicular lymphoma in five (10%) patients. The overall survival from the first diagnosis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-019-03778-9) contains supplementary material, which is available to authorized users.

✉ Emmanuel Gyan
emmanuel.gyan@univ-tours.fr

Thomas Chalopin
tomchalopin@gmail.com

Nicolas Vallet
nls.vallet@gmail.com

Flavie Arbion
F.ARBION@chu-tours.fr

Carole Barin
C.BARIN@chu-tours.fr

Emmanuelle Rault
E.RAULT@chu-tours.fr

Alban Villate
alban.villate@gmail.com

Martin Eloit
martin.eloit@hotmail.fr

Laurianne Drieu La Rochelle
l.drieularochelle@chu-tours.fr

Amélie Foucault
Amelie.foucault@etu.univ-tours.fr

Marjan Ertault
M.ERTAULT@chu-tours.fr

Caroline Dartigeas
c.dartigeas@chu-tours.fr

Lotfi Benboubker
l.benboubker@chu-tours.fr

Marie-Hélène Estienne
marie-helene.estienne-felix@chu-tours.fr

Jorge Domenech
jorge.domenech@univ-tours.fr

Olivier Hérault
olivier.herault@univ-tours.fr

Extended author information available on the last page of the article

(OS1) at 5 years was 82.4% (95% CI 72.1–94.3). The median overall survival from the second diagnosis (OS2) was 98 months (95% CI 44–NR) and 5-year OS2 was 58.7% (95% CI 45.5–75.7). Median progression-free survival from the second diagnosis (PFS) was 47 months (95% CI 27–NR) with 5-year PFS of 49% (95% CI 35.9–67). OS and PFS did not statistically differ between synchronous and sequential dual neoplasms. In this cohort, that the death relative risk (RR) was significantly lower if the second neoplasm appeared after more than 4 years following the first diagnosis (OR 0.37 (95% CI 0.16–0.90)). The *Hemo*^{2} *study* confirmed the rarity of dual hematological neoplasms. In this cohort, HL and FL were the most frequent combinations. Our results may support that synchronous and sequential dual neoplasms bear the same prognosis. Further studies are needed to better characterize these uncommon clinical situations.

Keywords Lymphoid · Myeloid · Sequential · Synchronous · Hematological neoplasm

Introduction

The coexistence of dual hematological neoplasms (HNs) is very rare, occurring in only 0.3 to 1.1% of patients [1–4]. It is an uncommon clinical situation which is complex to characterize and therapeutically challenging, for which the prognosis is unknown.

The literature is mainly focused on patients with chronic myeloid neoplasms (MNs). There is evidence that patients with MNs are at an increased risk to develop second primary hematological neoplasms relative to the general population [1, 2]. Concerning lymphoid neoplasms (LNs), chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma (HL) were shown to be associated with MNs [5–7]. Hauck et al. showed that the combination of CLL and JAK_2-negative MNs accounted for approximatively 50% of dual hematological malignancies in their population [3]. The coexistence of two different lymphomas is very rare [8]. Other LN and MN associations have only been described in reported cases.

Synchronous and sequential associations differ by 4 weeks between the two diagnoses [9]. Recently Kotchetkov et al. identified 46 patients with synchronous dual neoplasms, which represent a prevalence of 1.51% among patients diagnosed with any HN [9].

Interestingly, interactions between systemic autoimmune or chronic inflammatory diseases and hematological malignancies are reported. For example, patients with Sjogren syndrome have a 10.44-fold increase in risk of lymphoma than healthy population, higher than that reported for systemic lupus (sevenfold) or rheumatoid arthritis (fourfold) [10]. However, pathogenesis remains poorly understood; several studies suggest key role of prooncogenic factors in abnormal lymphomagenesis [11]. Other studies have indicated that patients with MNs have a higher risk of developing solid tumors [2, 12, 13]. Earlier work found an increased risk (60%) in patients with myeloproliferative neoplasms of nonhematologic malignancies compared with a matched control cohort [2]. However, these data are controversial and may require further biological studies [14].

The pathogenic mechanism underlying dual hematological neoplasms is unknown. A few studies have suggested that LNs and MNs may share a common clonal origin [15]. Pathogenic age-related clonal hematopoiesis (ARCH) mutations may have occurred in both LNs and MNs. Whole exome sequencing (WES) and next-generation sequencing (NGS) have already been used to explore these pathogenic mechanisms in dual hematological malignancies, and a potential key role played by noncanonical ARCH has been found [16–18].

We aimed to describe the clinical characteristics, treatments, and outcomes of patients with sequential or synchronous dual hematological malignancies. We evaluated the frequency of all combinations of lymphoid and myeloid neoplasms.

Material and methods

Cohort selection

We performed a retrospective review of all patients diagnosed with any HN in our department between 2007 and 2018 by searching through the medical records database of our institution. Inclusion criteria corresponded to the coding of two independent malignancies, confirmed by the World Health Organization 2016 criteria [19, 20]. We excluded patients with therapy-related myeloid neoplasms, the evolution of acute myeloid leukemia (AML), any transformation (multiple myeloma (MM) from smoldering myeloma or monoclonal gammopathy of uncertain significance (MGUS), or aggressive LNs from low-grade LNs), Richter's syndrome, and composite lymphoma. We also excluded patients who underwent solid organ transplant or those with an HIV/AIDS positive status.

We collected and analyzed relevant clinical, biological, and therapeutic data by reviewing the patients' medical records. This included age, sex, type and stage of disease, cytogenetic,

treatment, and status at follow-up. This study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee for human research (project Hemo^2 Study no. 2018-108).

Statistical analysis

For each patient, the time of follow-up was defined as the dates of the first and second neoplasm diagnosis to the date of last follow-up or death. For sequential associations, overall survival (OS) corresponded to the time of first (OS1) or second (OS2) neoplasm diagnosis to death. Progression-free survival (PFS) was defined as the time of second neoplasm diagnosis to relapse, progression, or death. For synchronous dual hematological malignancies, OS and PFS were defined as the time of diagnosis of both neoplasms to death for OS and relapse or progression for PFS. Data were analyzed using a descriptive methodology. The Kaplan-Meier and log-rank tests for survival analysis were performed using R software version 3.5.0.

Results

Patient characteristics

We first identified 1808 patients from the medical record database of our department. A total of 1641 patients were excluded because of error ($n = 567$) or different codings for the same neoplasm ($n = 1074$). Among the 188 remaining patients, 139 were not included due to evolution of AML from a previous myeloid malignancy ($n = 8$), therapy-related myeloid neoplasm ($n = 36$), any transformation ($n = 68$), Richter's syndrome ($n = 22$), and composite lymphoma ($n = 5$). Thus, 49 patients with confirmed dual hematological neoplasms were included (Fig. 1).

The prevalence of dual HN among all patients diagnosed and followed in our institution between 2007 and 2018 ($n = 5508$) was thus 0.89%.

Among the 49 included patients, sequential dual neoplasms were found in 36 (73%) and synchronous neoplasms in 13 (27%). Among patients with a sequential association, 23 (64%) had dual LNs, nine (25%) MN prior to LN, three (8%) LN prior to MN, and one (3%) dual MNs. Median time before diagnosis of the second neoplasm was 58 months (range 1.5–396.2). Among the remaining patients with synchronous diseases, seven (54%) had two LNs and six (46%) presented a concurrent LN and MN. Only one patient (2%) presented three different hematological neoplasms during his lifetime.

Cumulative incidence of sequential hematological neoplasm

Median cumulative incidence of a second hematological neoplasm was 6 years (95% CI 3–7) The 5-year cumulative incidence function (CIF) was 53.0% (95% CI 38.7–72.0) (Fig. 2). In patients with LN as first neoplasm, the 5-year CIF probability was 38.5% (95% CI 16.6–54.6), whereas it was 70.0% (95% CI 30.9–88.4) in those with MN as first neoplasm ($p = 0.059$).

Characteristics of hematological malignancies and clinical and biological characteristics

Forty-nine patients were included, which corresponded to a total of 99 HNs. Patients presented LNs in 80% of cases ($n = 79$ neoplasms) and MNs in 20% ($n = 20$ neoplasms). Those characteristics are shown in Table 1. The most common LNs were HL ($n = 16$, 16%), multiple myeloma ($n = 11$, 11%), CLL ($n = 10$, 10%), and T cell NHL ($n = 10$, 10%). Among patients with MNs, five (5%) had essential thrombocythemia and four (4%) had polycythemia vera and myelodysplastic syndrome.

Demographic, clinical, and biological characteristics and detailed information concerning the patients' treatment and clinical outcome are summarized in Table 2 and Supplementary Table S1. Sex ratio M/F was 1.88 with 32 males (65%) and 17 females (25%) (Supplementary Table S2). Among patients with cytogenetic analysis at the time of first diagnosis ($n = 27$; 55%), cytogenetic abnormalities (conventional and/or FISH) were found in 13 (48%). Two patients (7%) had abnormalities only for the second neoplasm. Five patients (18%) had new abnormalities at the time of second diagnosis. TP53 mutation was detected in only two patients who presented with CLL.

Dual hematological neoplasm combinations

The most frequent combination was follicular lymphoma (FL) and HL ($n = 5$, 10%), one patient with a synchronous diagnosis and four with sequential diagnoses (Fig. 3). An association between CLL and MNs was found in four (8%) patients (two synchronous and two sequential). Multiple myeloma was associated with CLL and T-NHL in four (8%) and two (4%) patients, respectively. T-NHL was also diagnosed with HL in three (6%) patients and with diffuse large B cell lymphoma (DLBCL) in two (4%).

Only one patient (2%) developed two sequential MNs, with systemic mastocytosis followed by chronic myelomonocytic leukemia (CMML).

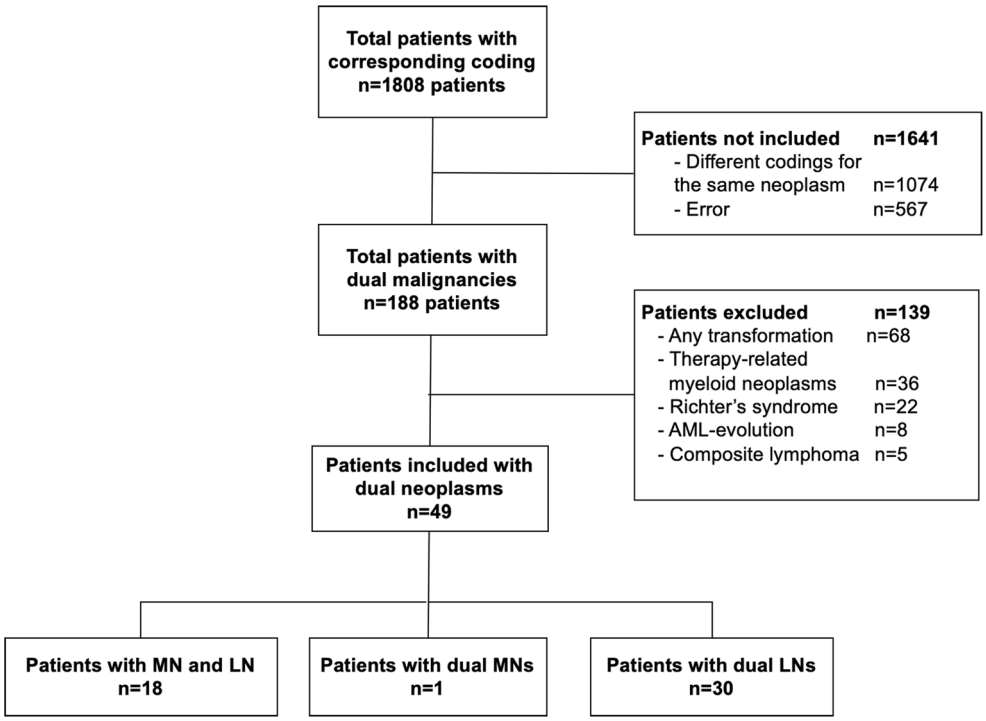

Fig. 1 Flow chart of the *Hemo*^{2} *study.* AML: acute myeloid leukemia; LN(s): lymphoid neoplasm(s); MN(s): myeloid neoplasm(s)

Treatment

Most patients received treatment for both hematological neoplasms (90%). The most frequent was chemotherapy (81%). Regimens used were considered to be standard: anthracycline-based in 41%, cisplatine or aracytine-based in 8%, immunomodulatory or proteasome inhibitory-based in 18%, palliative oral chemotherapy in 18%, fludarabine or bendamustine-based in 12%, and others in 3% (Supplementary Table S1).

Other strategies without chemotherapy, such as bleeding or immunosuppressive treatments, were administered in 5% of cases. Radiotherapy and surgery were performed in 2% each. Active monitoring was decided for 10% of patients, mainly for indolent LNs or nonevolutive MNs. At the time of diagnosis of the second neoplasm, the first malignancy was in complete remission in 61% of patients, stable in 31%, and in partial response in 8%.

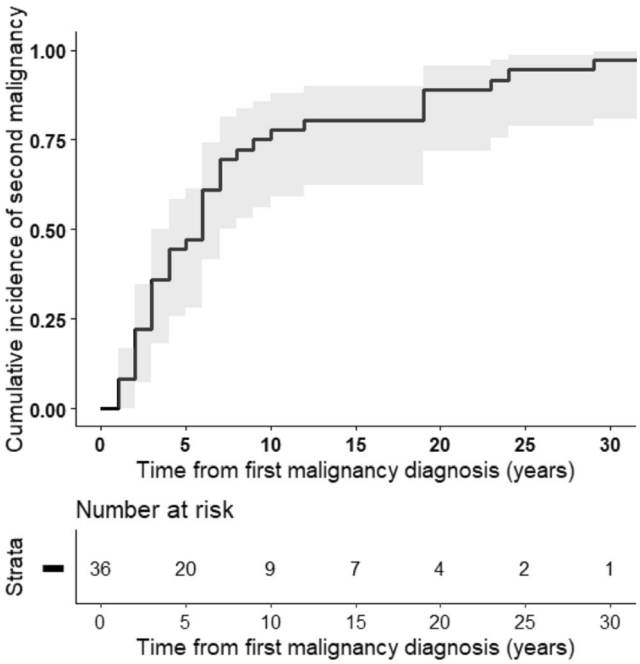

Fig. 2 Cumulative incidence function with 95% confidence intervals of second hematological neoplasm for the entire cohort

Details of solid tumor or chronic inflammatory disease associated

Concerning nonhematological neoplasms, 23 patients (47%) had at least one solid tumor associated. The most frequent diagnoses were squamous carcinoma ($n = 5$; 10%), basal carcinoma ($n = 4$; 8%), and breast cancer ($n = 4$; 8%) (Table 3). Most solid tumors occurred in patients with sequential dual LNs ($n = 14$; 61%). It was mainly associated with HL ($n = 9$; 39%), T-NHL ($n = 6$; 26%), and DLBCL ($n = 5$; 22%). We did not find significant association between hematologic neoplasm and a type of solid tumor. In all solid tumors associated, 31% were diagnosed before HN, 6% between, and 10% after both HNs. Among patients with solid tumor diagnosed before the first hematological neoplasm, we found standard treatment with surgery in 93% of cases, radiotherapy in 47%, and chemotherapy and hormonotherapy in only 20% of cases.

Table 1 Patient characteristics and associated myelo- and lymphoid neoplasms

	Overall cohort ($n = 49$ patients; $n = 99$ neoplasms)	Sequential malignancies ($n = 36$ (73%); $n = 73$ neoplasms)	Synchronous malignancies ($n = 13$ (27%); $n = 26$ neoplasms)
Sex			
Female	17 (35)	12 (33)	5 (38)
Male	32 (65)	24 (67)	8 (62)
Hematological malignancies			
Lymphoid prior to myeloid neoplasms	3 (6)	3 (8)	–
Myeloid prior to lymphoid neoplasms	9 (19)	9 (25)	–
Dual lymphoid neoplasms	30 (61)	23 (64)	7 (54)
Dual myeloid neoplasms	1 (2)	1 (3)	–
Lymphoid and myeloid neoplasms	6 (12)	–	6 (46)
Time between (months)			
Median	–	48	–
Range (min-max)	–	(1–396)	–
Lymphoid neoplasms, *n* (%)	79 (80)	59 (81)	20 (77)
Hodgkin lymphoma	16 (16)	13 (18)	3 (12)
Multiple myeloma	11 (11)	8 (11)	3 (12)
Chronic lymphocytic leukemia	10 (10)	6 (8)	4 (15)
T cell non-Hodgkin lymphoma	10 (10)	9 (12)	1 (4)
Follicular lymphoma	9 (8)	5 (7)	4 (15)
DLBCL	9 (8)	7 (8)	2 (8)
Marginal zone lymphoma	7 (7)	5 (7)	2 (8)
Hairy cell leukemia	3 (3)	2 (3)	1 (4)
Burkitt lymphoma	2 (2)	2 (3)	–
Mantle cell lymphoma	1 (1)	1 (1)	–
Waldenstrom macroglobulinemia	1 (1)	1 (1)	–
Myeloid neoplasms, *n* (%)	20 (20)	14 (19)	6 (25)
Myeloproliferative neoplasms, *n* (%)	12 (12)	10 (14)	2 (8)
Essential thrombocythemia	5 (5)	3 (4)	2 (8)
Polycythemia vera	4 (4)	4 (6)	–
Primary myelofibrosis	1 (1)	1 (1)	–
Chronic myeloid leukemia	2 (2)	2 (3)	–
Myelodysplastic syndrome	4 (4)	1 (1)	3 (12)
Mastocytosis	3 (3)	2 (3)	1 (4)
Chronic myelomonocytic leukemia	1 (1)	1 (1)	–

DLBCL diffuse large B cell lymphoma

Among our population, we found 22 patients (45%) with concomitant chronic inflammatory disease (CID) (Table 3). As in solid tumors, most patients were diagnosed with sequential dual LNs ($n = 12$; 55%). Eight patients (16%) were treated for an autoimmune disease, 7 (14%) for diabetes, 4 (8%) for thyroid dysfunction, and 3 patients (6%) for chronic obstructive bronchopneumopathy (details in Supplementary Table S3). CIDs were associated with CLL in 7 patients (32%), MM in 7 patients (32%), and HL in 6 patients (27%). In most cases, levothyroxine or insulin was used, and

Table 2 Characteristics, treatment, outcomes, and survival of patients depending on whether the association was sequential or synchronous

	Sequential ($N = 36$ (74%))								Synchronous ($N = 13$ (26%))	
	LN prior to MN ($N = 3$ (8%))		Both LNs ($N = 23$ (64%))		MN prior to LN ($N = 9$ (25%))		Both MNs ($N = 1$ (3%))		LN and MN ($N = 6$ (46%))	Dual LNs ($N = 7$ (54%))
	First LN	Second MN	First LN	Second LN	First MN	Second LN	First MN	Second MN		
Age (years)	69	73	61	68	62	68	83	88	70	70
Range (min-max)	(65–80)	(71–88)	(15–83)	(45–93)	(47–77)	(58–80)	NA	NA	(60–84)	(46–87)
Gender, female *n* (%)	1 (33)		7 (30)		3 (33)		1		3 (50)	2 (29)
Time between, median range (min-max) months	72 (48–98)		84 (24–396)		36 (18–120)		10 (NA)		NA	NA
Cytogenetic, *n* (%)										
With abnormalities	2 (66)	1* (33)	8 (35)	4* (17)	1 (11)	–	1	1	–	1 (14)
Normal	–	–	5 (22)	2 (9)	3 (33)	1 (11)	–	–	5 (83)	1 (14)
Not assessed	–	1 (33)	10 (43)	17 (74)	–	3 (33)	–	–	1 (17)	–
Solid tumor, *n* (%)	1 (33)		14 (61)		3 (33)		0		3 (50)	2 (28)
Chronic inflammatory disease associated, *n* (%)	2 (66)		12 (52)		3 (33)		1		1 (17)	3 (43)
Treatment, *n* (%)										
Chemotherapy	2 (67)	1 (33)	19 (83)	22 (96)	7 (78)	7 (78)	1	1	3 (50)	6 (86)
Radiotherapy	–	–	1 (4)	–	–	1 (11)	–	–	–	–
Surgery	–	–	–	–	1 (11)	1 (11)	–	–	–	–
Other**	–	1 (33)	–	–	1 (11)	–	–	–	2 (33)	–
Abstention	1 (33)	1 (33)	3 (13)	1 (4)	–	–	–	–	1 (17)	1 (14)
Response at time of second neoplasm, *n* (%)										
Complete response	0		18 (78)		3 (33)		1	–	NA	NA
Partial response	1 (33)		1 (4)		1 (11)		–	–		
Stable disease	2 (67)		4 (17)		5 (56)		–	1		

LN(s) lymphoid neoplasm(s), *MN(s)* myeloid neoplasm(s), *NA* not applicable

*With new cytogenetic abnormalities

**Immunosuppressive treatment, bleeding

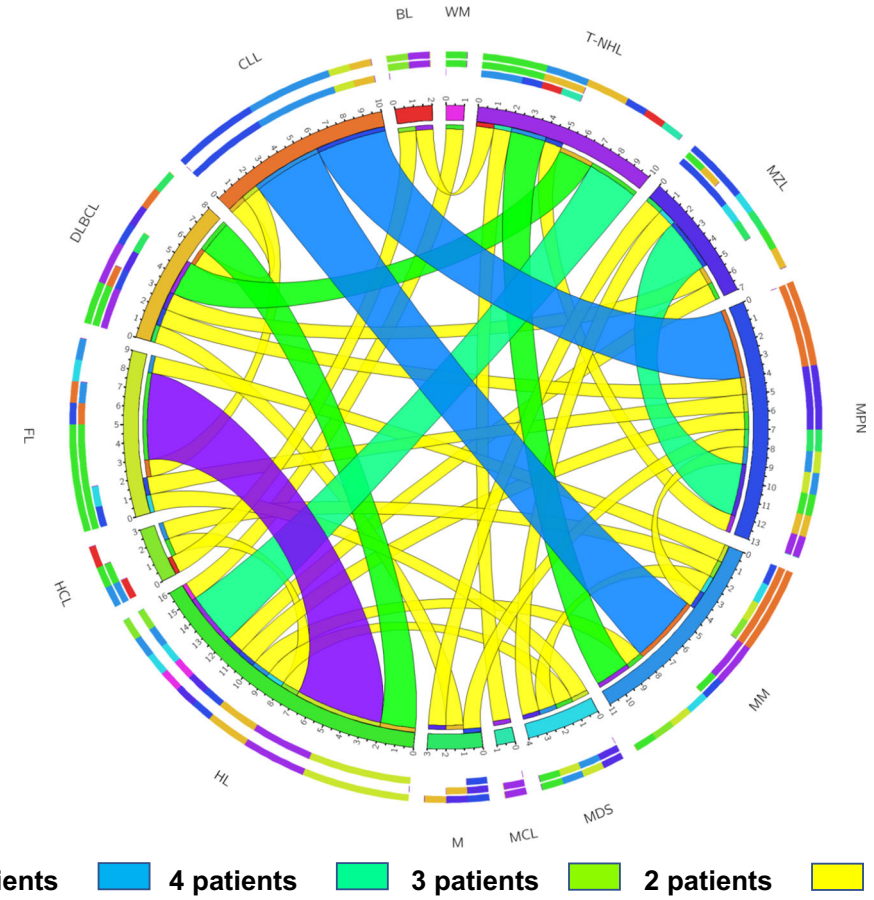

Fig. 3 Circos graph representing dual hematological malignancy combinations. BL: Burkitt lymphoma; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma; HCL: hairy cell leukemia; HL: Hodgkin lymphoma; M: mastocytosis; MCL: mantle cell lymphoma; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPN: myeloproliferative neoplasms; MZL: marginal zone lymphoma; T-NHL: T cell non-Hodgkin lymphoma; WM: Waldenstrom macroglobulinemia

none of these patients received specific treatment for autoimmune diseases. Median time to second neoplasm was 52.5 months (95% CI 36–95) for patients with CID and 34 months (95% CI 16–77) for patients without CID ($p = 0.78$).

Survival, relapse, and progression-free survival analysis

The median time of follow-up was 97 months (IQR 60–140) from the first diagnosis and 39 months (IQR 14–71) from the second. At the last follow-up, 23 (47%) patients died. The main causes of death were (i) progression ($n = 13$, 56%); (ii) cardiorespiratory failure ($n = 6$, 26%), and (iii) infections ($n = 4$, 18%).

Median PFS was 47 months (95% CI 27–NR), and 5-year PFS was 49% (95% CI 35.9–67) (Fig. 4a). Fourteen patients relapsed (29%), for whom 65% was lymphoid relapse and 35% myeloid relapse. There was no difference in median PFS according to whether relapse was lymphoid or myeloid, with 25 months (95% CI 7–NR) vs. 29 months (95% CI 26–NR), respectively ($p = 0.48$). Among the 14 relapses, eight (57%) involved the first neoplasm and six (43%) the second. Sequential and synchronous 5-year PFS did not statistically differ, with 48.3% (95% CI 33.7–69.3) and 49.8% (95% CI 26.1–95.3) ($p = 0.74$), respectively.

The median OS1 was not reached (NR), and the 5-year OS1 was 82.4% (95% CI 72.1–94.3). The median OS2 was 98 months (95% CI 44–NR), and 5-year OS2 was 58.7% (95% CI 45.5–75.7) (Fig. 4b, c). There was no statistically significant difference between OS2 for sequential and synchronous neoplasms with 57.9% (95% CI 43.0–77.7) and 60.6% (95% CI 36.2–100) at 5 years, respectively. If the second neoplasm occurred after more than 4 years following the first diagnosis, the relative risk (RR) of death was 0.37 (95% CI 0.16–0.90).

Concerning associated diseases, we found a statistical difference between patients with or without CID, with a median OS1 of 97 months (95% CI 82–NR) vs. 524 months (95% CI 286–NR), respectively ($p = 0.001$). Occurrence of solid tumors was not associated with a difference of OS in patients with double HN ($p = 0.93$).

Table 3 Details of patients with solid tumors or chronic inflammatory diseases associated

	Total ($n = 49$)	Hematological neoplasms	
		Sequential ($n = 36$)	Synchronous ($n = 13$)
Solid tumor associated, *n* (%)	23 (47)	18 (50)	5 (38)
Before hematological neoplasms	15 (31)	11 (31)	4 (33)
Between or during	3 (6)	3 (8)	0
After	5 (10)	4 (11)	1 (8)
Sex, *n* (%)			
Female	9 (18)	7 (19)	2 (15)
Male	14 (29)	11 (31)	3 (23)
Histologic type, *n* (%)			
Squamous carcinoma	5 (10)	5 (14)	0
Basal carcinoma	4 (8)	3 (8)	1 (8)
Breast	4 (8)	2 (6)	2 (15)
Sarcoma	2 (4)	1 (3)	1 (8)
Rectum	2 (4)	2 (6)	0
Colon	1 (2)	1 (3)	0
Uterus, prostate, endometrium, stomach, lung	1 each (2% each)	1 each (not prostate)	1 (8)
≥ Two solid tumors	2 (4)	2 (6)	0
Chronic inflammatory disease associated, *n* (%)	22 (45)	18 (50)	4 (31)
Sex, *n* (%)			
Female	4 (8)	3 (8)	1 (8)
Male	18 (37)	15 (42)	3 (23)
Type, *n* (%)			
Autoimmune disease	8 (16)	7 (19)	1 (8)
Diabetes	7 (14)	5 (14)	2 (15)
Thyroid dysfunction	4 (8)	3 (8)	1 (8)
Chronic obstructive bronchopneumopathy	3 (6)	3 (8)	0
Solid tumor associated, *n* (%)	12 (24)	12 (33)	0

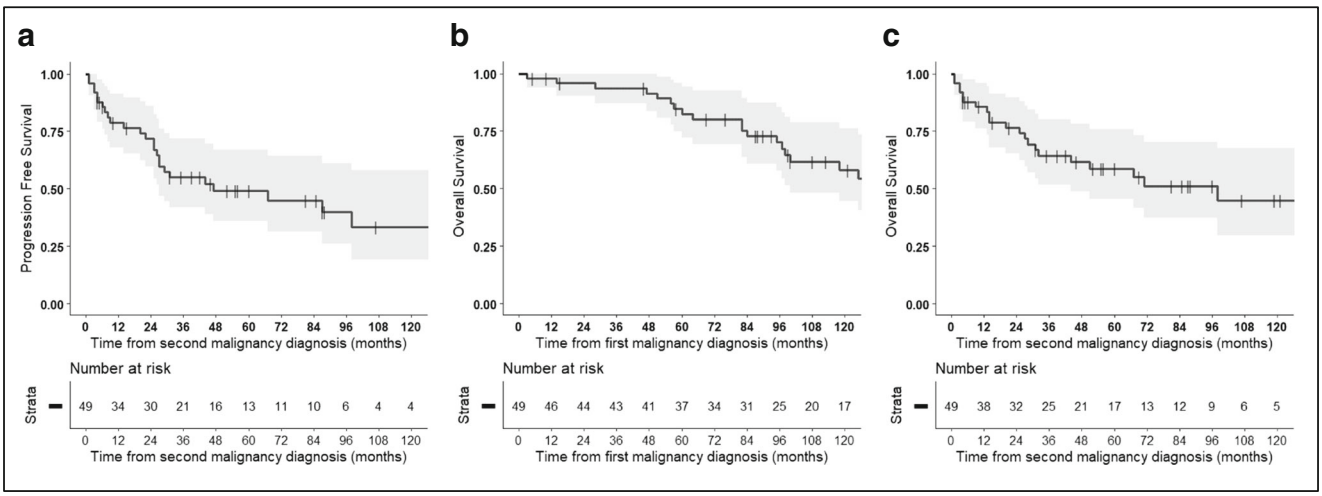

Fig. 4 Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS). **a** PFS for all included patients. OS from the first diagnosis (OS1) **(b)** and OS from the second diagnosis (OS2) (**c**) for all included patients

Discussion

Herein, we report the results of the *Hemo² study*, which aimed at describing and analyzing the characteristics of patients with dual hematological neoplasms, sequential in 73% and synchronous in 27%, while epidemiological data have already been published [1–4, 9]. For the first time, real-life cumulative incidence, survival, and outcome data are reported, including all HN combinations. The most frequently associated neoplasms were FL with HL, found in five patients.

In our center, the frequency of coexistent dual neoplasms was 0.89%. This finding is consistent with those of previous studies. Rumi et al. reported a prevalence of 1.1% of patients with MNs who developed LNs over their lifetime [1]. Hauck et al. showed a frequency of 1% of patients with MNs associated with LNs [3]. Kotchetkov et al. identified a prevalence of 1.51% [9] of synchronous dual neoplasms. High rate of males (65%) was found in our cohort, without significant association with any HN. In similar studies, sex ratio (M/F) varied from 0.8 to 2.14 [1–4, 9]. In a French nationwide epidemiologic study on cancer incidence over the 1980–2012 period, sex ratio (M/F) varied from 1.1 for classical Hodgkin lymphoma (vs. 1.66 in our cohort) to 4.0 for MCL [21]. It is unknown how sex ratio is associated with HN and particularly lymphoma.

Here, we identified mostly LNs (74%) for the first diagnosis. This differs from other series, which reported an increased risk of developing LNs in a population selected for myeloproliferative syndromes [1, 4–7]. Rumi et al. concluded that MN patients have a 2.79-fold higher risk (95% CI 1.8–4.3) to develop LNs [1]. Landtblom et al. also reported a hazard ratio (HR) of 2.6 (95% CI 2.0–3.3) for developing lymphoma in a large population of MNs patients [2]. The design of the study which included patients selected for one MN might explain this difference. In our study, patients were not selected for any primary neoplasm. We were thus able to identify every combination that occurred in our center. In the *Hemo² study*, 25% of patients presented sequential MNs prior to LN. Among patients with myeloid neoplasms, the most frequent association was MNs with CLL, in accordance with the literature, following by marginal zone lymphoma associated with MNs [6, 7]. We also found three patients with systemic mastocytosis with associated clonal hematologic nonmast cell lineage disease (SM-AHNMD). This entity is well defined as a common subtype of mastocytosis [19, 22, 23]. In our study, the AHNMD were CMML, MZL, and DLBCL, which are consistent with the literature [24, 25]. Several studies suggest a common precursor in SM-AHNMD with KIT involvement, but other mutations were often detectable in TET2, ASXL1, RUNX1, or RAS [26].

In our series, LNs were heterogeneous, with aggressive (70%) or indolent disease (30%). We also report the largest number of HL coexistent with FL ($n = 5$; 10%). This is the first report to describe this combination. In contrast, composite lymphoma composed of HL and FL has been recorded sporadically [27, 28]. This suggests a common germinal center B cell between both lymphomas [29, 30].

We observed that second neoplasms appeared several years after the first diagnosis, with a median CIF of 6 years. Cumulative incidence analysis did not show a difference between hematological neoplasm types at first diagnosis (LN or MN). Recently, Kotchetkov et al. described a cohort of 46 patients with synchronous dual hematological neoplasms [9]. They found that management can be similar to that for a single hematological malignancy. The therapy should thus be targeted to the most aggressive neoplasm to control it. Most of our patients required curative treatment for MNs or LNs. Importantly, the treatment strategy used in our cohort was almost the standard choice for both neoplasms. The clinical course of the second diagnosis was not influenced by the first response to treatment. Myeloid or lymphoid relapse occurring after the second diagnosis had no impact on survival, with a short follow-up. In contrast, the occurrence of second neoplasms during the 4 years following the first diagnosis increased the risk of death relative to those diagnosed later.

We found a high rate of patients with CID ($n = 22$, 45%). Chronic stimulation by immune complexes or proinflammatory cytokines could be a key event involved in lymphomagenesis [11]. Mechanisms that control B cell activation could be dysregulated and less efficient in tissues. Moreover, signaling pathways, such as NF-kB, involved in both autoimmune and lymphoid diseases, would be compromised in immunosurveillance mechanisms.

Twenty-three (47%) patients showed associated nonhematological neoplasms. Several mechanisms are possible, including the degree of immunosuppression induced by the treatment or neoplasm itself, cytoreductive treatment, genetic predisposition, or acquired mutations. Landtblom et al. reported a significantly increased risk of solid tumors in a population of MNs patients, with a HR of 1.6 (95% CI 1.5–1.7) [2]. In the study of Kotchetkov et al., 30% of patients with synchronous double disease had at least one concomitant solid tumor, especially in dual LN cases (64%) [9].

The main weakness of our study was obviously the small size of the cohort. Furthermore, relevant biological data were missing, such as cytogenetic or histologic subtypes, due to the retrospective nature of this study.

The rarity of dual disease may impede any further prospective studies. Future biological investigations are warranted to decipher the pathogenic mechanism, especially to compare the clonal origins.

In conclusion, the *Hemo² study* confirms that dual hematological neoplasms are uncommon. We described all combinations in our cohort in which LH and LF were the most frequent. Second primary hematological malignancy may not affect PFS or OS. We also find a significant proportion of

patients with chronic inflammatory diseases or solid tumors. Finally, our findings showed that although the median CIF of second hematological neoplasm was 6 years, its occurrence within the 4 years after first diagnosis was associated with shorter OS. This may suggest that hematologists should remain vigilant during follow-up, particularly in the first 4 years following the first diagnosis.

Authors' contributions TC, NV, and EG collected, analyzed, and interpreted data, and wrote the manuscript. NV performed statistical analysis. FA, CB, ER, AV, ME, LDR, AF, ME, CD, LB, MHE, JD, and OH contributed essential tools and revised and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the ethical committee in human research of the Hospital of Tours (project Hemo^2 Study no. 2018-108).

References

1. Rumi E, Passamonti F, Elena C, Pietra D, Arcaini L, Astori C, Zibellini S, Boveri E, Pascutto C, Lazzarino M (2011) Increased risk of lymphoid neoplasm in patients with myeloproliferative neoplasm: a study of 1,915 patients. Haematologica. 96(3):454–458
2. Landtblom A-R, Bower H, Andersson T et al (2018) Second malignancies in patients with myeloproliferative neoplasms: a population-based cohort study of 9379 patients. Leukemia. 32(10):2203–2210
3. Hauck G, Jonigk D, Kreipe H, Hussein K (2013) Simultaneous and sequential concurrent myeloproliferative and lymphoproliferative neoplasms. Acta Haematol 129:187–196
4. Masarova L, Newberry K, Pierce S et al (2015) Association of lymphoid malignancies and Philadelphia-chromosome negative myeloproliferative neoplasms: clinical characteristics, therapy and outcome. Leuk Res 39:822–827
5. Todisco G, Manshouri T, Verstovsek S, Masarova L, Pierce SA, Keating MJ, Estrov Z (2016) Chronic lymphocytic leukemia and myeloproliferative neoplasms concurrently diagnosed: clinical and biological characteristics. Leuk Lymphoma 57(5):1054–1059
6. Laurenti L, Tarnani L, Nichele I et al (2011) The coexistence of chronic lymphocytic leukemia and myeloproliferative neoplasms: a retrospective multicentric GIMEMA experience. Am J Hematol 86(12):1007–1021
7. Palandri F, Derenzini E, Ottaviani E et al (2009) Association of essential thrombocythemia and non-Hodgkin lymphoma: a single-centre experience. Leuk Lymphoma 50(3):481–484
8. Oka K, Nagayama R, Yonekawa N, Nihei T, Sando N, Yatabe Y, Mori N (2012) Concurrent gastric MALT and Hodgkin lymphoma: a case report. Int J Surg Pathol 20(2):201–204
9. Kotchetkov R, Ellison E, McLean J, Pressnail B, Nay D (2018) Synchronous dual hematological malignancies: new or underreported entity? Hematology. 23(9):596–599
10. Zintzaras E, Voulgarelis M, Moutsopoulos HM et al (2005) The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 165(20):2337–2344
11. Nocturne G, Mariette X (2015) Sjögren syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol 168(3):317–327
12. Frederiksen H, Farkas DK, Christiansen CF, Hasselbalch HC, Sorensen HT (2011) Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study. Blood. 118(25):6515–6520
13. Khanal N, Giri S, Upadhyay S, Shostrom VK, Pathak R, Bhatt VR (2016) Risk of second primary malignancies and survival of adult patients with polycythemia vera: a United States population-based retrospective study. Leuk Lymphoma 57(1):129–133
14. Susini MC, Masala G, Antonioli E, Pieri L, Guglielmelli P, Palli D, Bosi A, Vannucchi AM (2012) Risk of second cancers in chronic myeloproliferative neoplasms. Blood. 119(16):3861–3862
15. Salmoiraghi S, Montalvo MLG, D'Agostini E et al (2013) Mutations and chromosomal rearrangements of JAK2: not only a myeloid issue. Expert RevHematol 6(4):429–439
16. Damm F, Mylonas E, Cosson A, Yoshida K, Della Valle V, Mouly E, Diop M, Scourzic L, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Kikushige Y, Davi F, Lambert J, Gautheret D, Merle-Beral H, Sutton L, Dessen P, Solary E, Akashi K, Vainchenker W, Mercher T, Droin N, Ogawa S, Nguyen-Khac F, Bernard OA (2014) Acquired initiation mutations in early hematopoietic cells of CLL patients. Cancer Discov 4(9):1088–1101
17. Agathangelidis A, Ljungström V, Scarfo L et al (2018) Highly similar genomic landscapes in monoclonal B-cell lymphocytosis and ultra-stable chronic lymphocytic leukemia with low frequency of driver mutations. Haematologica. 103(5):865–873
18. Henry L, Carillo S, Jourdan E, Arnaud A, Brun S, Lavabre-Bertrand T (2007) Association of essential thrombocythemia and chronic lymphocytic leukemia: absence of the V617F JAK2 mutation in the lymphoid compartment. Am J Hematol 82(6):500–501
19. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 127(20):2391–2405
20. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision to the World Health Organization classification of lymphoid neoplasms. Blood. 127(20):2375–2390
21. Le Guyader-Peyrou S, Belot A, Maynadié M et al (2016) Cancer incidence in France over the 1980-2012 period: hematological malignancies. Rev Epidemiol Sante Publique 64(2):103–112
22. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, McClure RF, Li CY, Pardanani A (2009) Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 113(23):5727–5736
23. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, Sotlar K, Sperr WR, Escribano L, George TI, Kluin-Nelemans HC, Ustun C, Triggiani M, Brockow K, Gotlib J, Orfao A, Schwartz LB, Broesby-Olsen S, Bindslev-Jensen C, Kovanen PT, Galli SJ, Austen KF, Arber DA, Horny HP, Arock M, Metcalfe DD (2017) Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. Cancer Res 77(6):1261–1270
24. Pullarkat VA, Bueso-Ramos C, Lai R, Kroft S, Wilson CS, Pullarkat ST, Bu X, Thein M, Lee M, Brynes RK (2003) Systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease: analysis of clinico- pathologic features and activating c-KIT mutations. Am J Hematol 73(1):12–17
25. Pardanani A (2016) Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. Am J Hematol 91(11):1146–1159
26. Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, Sotlar K, Horny HP, Metzgeroth G, Kluger S, Naumann N, Haferlach C, Haferlach T, Valent P, Hofmann WK, Fabarius A,

Cross NCP, Reiter A (2016) Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. Leukemia. 30(1): 136–143
27. Papoudou-Bai A, Marinos L, Papathanasiou K et al (2018) Simultaneous presence of follicular, diffuse large-B cell lymphoma and Hodgkin-like lymphoma. Turk J Haematol 35(4):308–309
28. Fischer T, Zing NPC, Chiattone CS, Federico M, Luminari S (2018) Transformed follicular lymphoma. Ann Hematol 97(1):17–29
29. Brauninger A, Hansmann ML, Strickler JG et al (1999) Identification of common germinal-center B-cell precursors in two patients with both Hodgkin's disease and non-Hodgkin's lymphoma. N Engl J Med 340(16):1239–1247
30. Marafioti T, Hummel M, Anagnostopoulos I, Foss HD, Huhn D, Stein H (1999) Classical Hodgkin's disease and follicular lymphoma originating from the same germinal B cell. J Clin Oncol 17(12): 3804–3809

Affiliations

Thomas Chalopin[1] · Nicolas Vallet[1] · Flavie Arbion[2] · Carole Barin[3] · Emmanuelle Rault[4] · Alban Villate[1] · Martin Eloit[1] · Laurianne Drieu La Rochelle[1] · Amélie Foucault[4] · Marjan Ertault[1] · Caroline Dartigeas[1] · Lotfi Benboubker[1] · Marie-Hélène Estienne[4] · Jorge Domenech[4,5] · Olivier Hérault[4,5] · Emmanuel Gyan[1,5,6]

[1] Department of Hematology and Cell Therapy, University Hospital of Tours, 2 Boulevard Tonnellé, 37044 Tours Cedex 9, France

[2] Department of Pathology, University Hospital of Tours, Tours, France

[3] Department of Cytogenetics, University Hospital of Tours, Tours, France

[4] Department of Biological Hematology, University Hospital of Tours, Tours, France

[5] University of Tours, CNRS ERL 7001 LNOx and EA 7501, Tours, France

[6] Clinical Investigation Center, University Hospital of Tours, INSERM U1415, Tours, France