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Acute Myeloid Leukaemia following Direct Acting Antiviral drugs in HCV-infected patients: a 10 years' retrospective single-center study

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ABSTRACT

Background

After several cases of peculiar hematological malignancies following introduction of new oral anti-hepatitis C virus (HCV) treatments in our recent practice, we aimed to systematically identify all cases of hematological malignancies (HM) in patients with chronic HCV infection and to compare them according to the prescription of oral anti-HCV Direct Acting Antivirals (DAA) treatment or not.

Material/methods:

In this single-center retrospective observational study, we included all patients with confirmed HM and chronic HCV infection managed between 2010 and 2019 in the Pitié-Salpêtrière hospital, Paris. Non-inclusion criteria were a benign hematological disorder, an HM preceding chronic HCV infection and HCV acute infection. We compared characteristics of patients who received DAA before HM diagnosis to those with no DAA before HM.

Results: Over the 10 years, 61 cases of HM among HCV infected patients were identified (female 29%, median age of 58.0 years [IQR 17]). Twenty-one received DAA before the onset of HM (Group DAA+) and 40 did not (Group DAA-) including 22 having received DAA after HM. In the DAA+ group, oral NS5B, NS5A and NS3A inhibitors were used in 90, 76 and 29% respectively. HM developed in the two years following DAA initiation in 76%. Eight (38%)

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had Non-Hodgkin Lymphoma, 5 (24%) had an Acute Myeloid Leukaemia (AML) including two with a mixed phenotype, 2 each had Hodgkin Lymphoma, Multiple Myeloma or a myeloproliferative disorder and one each had a chronic Lymphocytic Leukaemia or AL Amyloidosis. In the Group DAA–, HM were NHL in 20(50%) patients, Myeloproliferative neoplasms in 7 (17%) , Multiple Myeloma in 5, Hodgkin Lymphoma in 3, Myelodysplastic syndrome and AML in 2 (5%) each and Acute Lymphoblastic Leukaemia in one. No significant difference between the groups DAA + and – was found according to age, sex, HCV genotype, viral load, co-infection or type and exposition of previous HCV treatments. AML, liver transplantation and cirrhosis were significantly more frequent in the DAA+ group (p = 0.020, 0.045 and 0.032, respectively).

Conclusion

AML seemed more frequent after using DAA treatments, notably in severe HCV patients including cirrhotic and/or liver transplanted patients. A multicentric observational study is ongoing to confirm and explore the results.

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KEYWORDS

Hepatitis C virus

Hematological malignancies

Direct Acting Antivirals

Acute Myeloid Leukaemia

Mixed-phenotype Acute Leukaemia

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INTRODUCTION

Chronic hepatitis C virus infection (HCV) remains a global public health concern affecting an estimated 71.1 million (62.5–79.4) individuals worldwide with mortality four times higher compared to general population (1-3).

The interferon-free direct antiviral agents (DAA), first used in 2011, have been a major milestone in the HCV infection treatment due to their efficacy including on severe cirrhosis or liver transplantation and their few side effects (4). Since 2016, the World Health Organization recommends DAA as a first-line treatment without interferon for every chronic HCV infection (5). DAA related viral eradication may result in a decreased risk of HCV related B-cell lymphoma and possible regression of HCV related Non-Hodgkin Lymphoma (NHL) (6, 7). However, several studies have suggested an increased early occurrence or recurrence of hepatocellular carcinoma after DAA use, raising concerns about safety and oncogenicity (8, 9). Nonetheless, these new insights have not been confirmed by other studies including meta-analyses (10). Even though HCV infection and liver transplantation are known risk factors for hematological malignancies (HM), predominantly of the B-cell type (4, 11, 12), some recent case studies suggest a possible increase in hematological disorders secondarily to DAA administration (13-17), which is consistent with our own experience.

This retrospective study aimed to identify and describe all cases of hematological malignancies (HM) in patients with chronic HCV infection in hematology or hepatology units in our hospital

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and to compare characteristics of patients according to the prescription of oral anti-HCV Direct Acting Antivirals (DAA) treatment or not.

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

This is a single-center retrospective observational study.

IDENTIFICATION OF RELEVANT PATIENTS

Every adult patient with a HM and a chronic hepatitis C infection managed between 01/01/2010 and 28/03/2019 in the hematology and/or hepatology departments of the Pitié-Salpêtrière hospital, in Paris, France was eligible. HM were defined according to WHO classifications. Chronic HCV infection was defined as an infection lasting for at least 6 months according to the hospital chart with at least one available HCV viral load. Patients were identified through the list of in- and outpatients managed in the hematology or in the hepatology departments. Non-inclusion criteria were HCV acute infection, benign hematological disorder and HM preceding HCV. In patients with a first HM, a minimal period of remission of 1 year before DAA administration was necessary to get included. Patients with a diagnosis of HM < 3 months following DAA initiation were also excluded. This arbitrarily limits the risk of including a patient with relapsing or subclinical HM at the initiation of DAA. The retrospective analysis of anonymized data is allowed by French law and all the patients during their medical care were informed of their right to refuse that their data may be used for research purpose. Our study was locally registered according to the General Data Protection

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Regulation. All cases with a HM after a treatment using DAA were declared to the local pharmacovigilance centre.

We evaluated whether eligible patients had received DAA and if so, we recorded the date of dispensation from the database provided by the Pitié-Salpêtrière pharmacy department.

Eligible patients were classified in 2 groups according to the sequence between DAA treatment and HM: Group DAA+ included patients who initiated their first DAA at least 3 months before HM diagnosis. Group DAA– included patients with no DAA before HM.

DATA EXTRACTION

The following detailed information was retrospectively collected from the medical charts of each patient:

- Socio-demographic data including sex and age

- Characteristics of the HCV infection: genotype, viral load at time of MH diagnosis, HIV or HBV co-infection, severity of liver disease according to the combination of noninvasive tests (Fibroscan® and/or Fibrotest®) or to a liver biopsy, hepatocellular carcinoma diagnosis.

- Date of liver transplantation if applicable

- Past HCV treatments including interferon, pegylated interferon or ribavirin use, with date and duration for each and DAA treatments with the type of combo drugs (NS5B, NS5A and NS3A inhibitors).

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- Risk factors for malignant hemopathy: hematological disease at risk, past exposure to chemo- or radiotherapy, AIDS, solid organ transplantation or other immunosuppression.

- Hematological malignancy: type, date of diagnosis, time between the first administration of DAA and occurrence of the HM, duration of follow up after HM diagnosis, treatment including bone marrow transplantation, outcome (survival or death).

STATISTICAL ANALYSES

We compared baseline characteristics, types of HM and outcomes in consecutive HCV patients with a HM diagnosis according to previous DAA therapy or not. As the hepatology unit proposed many anti-HCV DAA protocols since 2011 and the patients could have been treated with two or more DAA lines, we decided not to make a comparison by periods to limit the risk of an analytic bias.

STATISTICAL METHODS

All statistical analyses were done using RStudio Version 1.0.153. (R Core Team (2020). Patient characteristics were described as numbers and percentages for categorical data and as medians with interquartile range (IQR) for quantitative variables. Quantitative variables were compared using the Wilcoxon-Mann-Whitney test; qualitative variables were compared by the Chi2 test or the Fisher's exact test as appropriate. Survival times since diagnosis of HM were compared

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between groups DAA+ and DAA- using a Kaplan Meier curve and Cox test. A *p*-value < 0.05 was considered statistically significant. Cut-off date for data collection was 23/12/2020.

RESULTS

SELECTION PROCESS

From the 15,842 patients managed in the hematology department and the 3,499 patients managed in the hepatology department between 01/01/2010 to 28/03/2019, we identified 164 potentially eligible patients. From these, 103 patients were excluded mainly for a benign hematological disorder (n = 49), or the absence of chronic HCV infection (n = 22) (Figure 1 and Supplemental data 1). Finally, 61 patients had a history of HM and chronic VHC infection and were included in this study. All but four were followed in the hematology department of our hospital.

Twenty-one patients had a history of DAA use before HM diagnosis and were included in the DAA+ group. The DAA- group comprised 40 patients, having a history of chronic HCV infection without any DAA prior to HM diagnosis with 18 patients that never received any DAA and 22 having received DAA following HM diagnosis. Detailed information can be found in Table 1.

PATIENT CHARACTERISTICS

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Among the 61 HCV positive patients identified with HM, 29% were female with a median age at diagnosis of HM of 58 years [IQR 17]. HCV genotype 1 represented 60% of the cohort. Nine patients had an HIV infection, 2 an HBV co-infection. There was no significant difference between DAA + and DAA- groups, including age, sex, HCV genotype or viral load, co-infection, ALT levels, F Metavir stage at baseline, except for history of cirrhosis and liver transplantation which were significantly more frequent in the DAA+ group (52% vs. 30%, *p* = 0.032 and 38% vs. 12.5%, p = 0.045, respectively).

ANTI-HCV TREATMENTS

Type of previous anti-HCV treatments is detailed in Table 1. Groups were not significantly different in type and exposition of first line anti-HCV treatments with interferon and/or ribavirin. Five of 21 patients in the DAA+ group received at least 2 DAA treatment lines with the first line combining DAA with ribavirin (n = 2) or ribavirin + interferon (n = 3). NS5B, NS5A and NS3A inhibitors were part of the last all oral DAA combo treatments in 90, 76 and 29% respectively (Supplemental data 2). Median exposition time to DAA was 3 months [IQR 3]. Median time between initiation of DAA and HM diagnosis was 16.5 months [IQR 20.5] with all HM diagnosed within 6 years after DAA exposure including 3/4 in the first 2 years following DAA initiation.

TYPE OF HEMATOLOGICAL MALIGNANCIES

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Of the 21 patients in the DAA + group, 8 (38%) had a NHL, including 4 EBV induced Post Transplantation Lymphoproliferative Disease, vs. 20 NHL (50%) in the DAA- group (p = 0.42). Surprisingly, 5 (24%) patients in the DAA+ group had acute myeloid Leukaemia (AML) vs. only 2 (5%) in the DAA- group, with a significant difference (p = 0.02). While both DAA- patients with AML had previous HM known as risk factor, 3 of 5 DAA+ patients with AML had no specific risk factor including 2 with a Mixed-phenotype Acute Leukaemia (MPAL), a rare and poor-prognosis Leukaemia. Finally, 4 of the 5 DAA+ AML patients developed their HM in the first 3 years following successful DAA combo therapy. All five received a NS5B inhibitor (sofosbuvir). One of the 2 patients with mixed-phenotype acute Leukaemia had the highest number of DAA treatment lines (3) and the largest total duration of sofosbuvir (9 months).

RISK FACTORS FOR HEMATOLOGICAL MALIGNANCIES

In the DAA+ group, only 2 of the 21 cases were associated with a delayed recurrence of a NHL at 4 years and a multiple myeloma at eight years. Among the 19 patients with first onset HM, ten patients (47%) had at least one risk factor for developing HM including:

- Long term immunosuppressive treatments for renal (n = 1, tacrolimus) or liver transplantation (n = 6), for a mean duration of 6 years before HM.

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- HIV infection in 2 patients who developed Hodgkin Lymphoma, with a CD4 count of 168 and 1121/m3 respectively.

- Predisposing hematologic condition prior to DAA (cf. Table 1 Part B) (n=5)

Comparing patients with and without DAA, as described in the Table 1, Part A, proportion of previous hemopathy at risk (benign or malignant) or past chemo or radiotherapy were not different between groups. Concerning patients on chronic immunosuppressive treatments, although proportions of transplanted patients were similar between groups, we found that liver transplanted patients were more frequently found in the DAA group of patients. To note, no congenital risk factor was described in both groups.

OUTCOME

As DAA were authorized only in 2012, follow up was shorter in the DAA+ group with a median post HM-follow up time of 21.1 vs. 42.6 months (p = 0.024). At the cut-off date (23/12/2020), in the DAA+ group, one patient did not require specific treatment, one was lost to follow up, four achieved remission, six had stabilized their HM under treatment including 2 stem-cell transplantations (allogenic, n=1 and autologous, n=1) and nine died. Four of the five AML cases in the DAA+ group died. Nonetheless, outcomes as blood marrow transplantation requirement and mortality according to the Kaplan-Meier curves (Figure 2) did not

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significantly differ between group DAA+ or - but it should be noted that the follow-up time was shorter in the DAA+ group.

DISCUSSION

We described a total of 61 cases of HM in patients with a chronic HCV infection including 21 HM cases developing after the use of DAA. Our study highlights the following points for the patients using DAA: (1) types of HM seemed to differ when comparing patients with or without previous DAA, with a significant higher proportion of AML cases among patients following DAA therapy.

(2) Of the 5 AML in the DAA+ group, three including two rare cases of Mixed-phenotype Acute Leukaemia had no recognized risk factors.

(3) Three quarter of HM cases in the DAA treated patients occurred within two years after the use of DAA.

To the best of our knowledge, no AML cases after DAA treatment have been reported yet. The difference in frequency between the 2 groups of patients concerning the history of cirrhosis or liver transplantation may represent a confusion bias, yet these characteristics have to date never been associated with a higher risk of AML in the literature. Interestingly two of the five cases of AML in the group DAA+ were of mixed-phenotype meaning that they present morphologic and/or immunophenotypic characteristics of both myeloid and lymphoid lineages. These

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MPAL usually represent only 4 to 8% of all acute Leukaemias and present an aggressive clinical course, low complete remission and high recurrence rate (13). Both cases developed in liver transplanted patients, although MPAL is not currently associated with solid organ transplants nor immunosuppressive therapy. Therefore, our findings are quite astonishing and need to be investigated by further studies. Furthermore, it may be of interest to know, that one DAA + liver-transplanted case, with a NHL following DAA therapy treated by anthracyclines developed secondarily an AML not registered in our study as developed after the cut-off date. Previously described cases of HM following sustained viral response with DAA treatment remain spare but start to seek for awareness: To the best of our knowledge, no AML cases and only six cases of either early occurrence or relapse of NHL have so far been described (14-18). They occur in a time interval between 1 – 19 months after DAA treatment. None of these patients had a liver transplantation.

Aside from liver transplantation, chronic hepatitis C infection is also known to be associated with an increased risk of developing HM predominantly of B-cell type but not AML, whatever the level of liver fibrosis (4, 11, 12, 19). The underlying pathogenesis is most likely the chronic and continuous antigen stimulation leading to a permanent B-cell response with subsequent genetic mutation and finally clonal and malignant B-cell proliferations (20). Another possible explanation could be permanent B-cell damage induced either by HCV-derived viral protein

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production inside B-cells or the transient intracellular infection (21). Viral eradication results in hematological response in NHL in about two thirds of the cases suggesting a possible causal connection between the HCV infection and the occurrence of lymphoma (22). Discordant results were recently highlighted according to the influence of DAA on hematological risk compared to the general population. A retrospective cohort study found a prevalence of NHL after HCV DAA that was still 30-fold higher, (23). Another study points out that HCV viral eradication with DAA may not be associated with a reduction in NHL risk in HCV population. compared to the global population (24). Another one shows the disappearance of any higher risk for all hematological cancer following DAA therapy (25). We also found B-cell type lymphoma in cured HCV infections with DAA but at a weaker incidence than in patients without DAA, which is consistent with a potential protective effect of viral eradication at an early stage of the chronic infection, limiting the chronic inflammation and the risk of developing lymphoma.

No formal hypothesis emerged yet for the cases of HM cases described. The persistence of CD4 regulatory T cells, inhibiting CD8+ T-cells may be associated with a higher risk of developing HM (26). Recently a study pointed a high level of vascular endothelium growth factor (VEGF) after DAA treatment, which may accelerate tumor growth (27). Unfortunately, no VEGF assay was performed in our cohort to corroborate this hypothesis.

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Our study has several strengths. Hospital distribution of DAA allows capturing all patients having received DAA since its authorization. We were able to analyse both hepatology and haematology medical records for each patient, assure a long follow up duration and considered multiple several confusion factors. We have been careful not to omit patients who have benefited from treatment outside our hospital. But our study has limitations. First, information collection was retrospective and therefore missing data or incorrect data may be an issue but no variable exceeded 10% missing data. The number of included patients remains extremely small which could result in a possible lack of power. No multivariate analysis was performed because of the limited sample size and influence of a specific DAA could not be specifically evaluated. According to univariate analysis, potential confounding factors may exist in our study as patients in the DAA+ group had shorter follow-up time, more severe fibrosis/cirrhosis and/or liver transplantation. However, all these factors are not known to be associated with AML. Finally, we compared two groups of patients from different time sequences as DAA treatment was progressively used in different schemes starting end of 2011. Therefore, our results need to be taken with precaution and future larger studies are needed.

CONCLUSION:

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

In this comparative, retrospective and single-center study, we found, among HM in consecutive HCV patients, an unexpected proportion of AML in patients treated with DAA treatment compared to patients without DAA. AML cases included two rare mixed-phenotype forms. Further studies including an ongoing multicentric observational study to confirm and explore the results.

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IMPLICATIONS

CS and PL conceived the study.

EL, DAA and DRW helped with the acquisition of data

AD helped with the study design

All authors helped for the critical revision for important intellectual content and have approved the final article.

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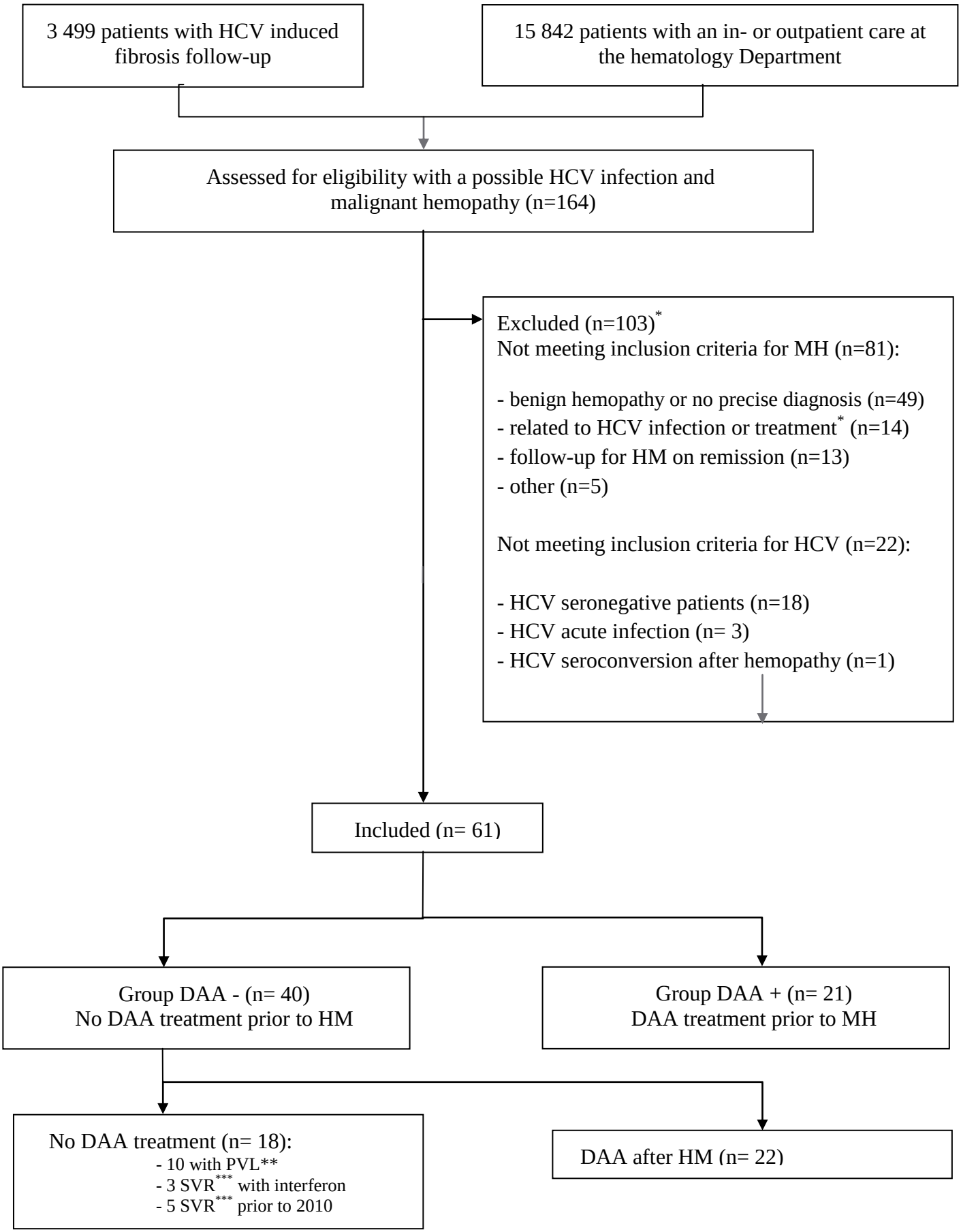
Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Figure 1: Flow Chart Diagram explaining the constitution of our groups



* Detailed information can be found in the appendix, **PVL Persistent viral load, ***SVR, Sustained viral remission, HM= Hematological malignancy

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Table 1: Overall characteristics and per group

Part A

	Total (n=61)	Group DAA – (n = 40)	Group DAA+ (n = 21)	p-value
Age*	58.0 (17)	55.0 (14)	63.0 (17)	0.121
Female	18 (29.5%)	11 (27.5%)	7 (33.3%)	0.769
Co-infections				
HIV +	9 (14.8%)	7 (17.5%)	2 (9.5%)	0.473
HBV+	2 (3.3%)	2 (5.4%)	0 (0%)	1
Chronic hepatitis C				
All Genotypes				0.670
1	37 (60.7%)	21 (52.5%)	16 (76.5%)	
2	2 (3.3%)	1 (3%)	1 (4.8%)	
3	8 (13.1%)	6 (17%)	2 (9.5%)	
4	8 (13.1%)	6 (17%)	2 (9.5%)	
Unknown	6 (9.8%)	6 (15.0%)	0 (0%)	
Interferon treatment	34 (55.7%)	20 (50.0%)	14 (66.7%)	0.576
Time to HM diagnosis (y)**	8.3 (7.9)	5.8 (7.7)	12.1 (8.4)	**0.020**
Treatment duration (m)	12.0 (9.5)	9.50 (6.8)	14.0 (17.5)	0.100
Ribavirin treatment	38 (62.3%)	23 (57%)	15 (76.2%)	0.256
Time to HM diagnosis (y) **	8.0 (8.0)	6.3 (8.1)	9.9 (7.2)	0.100
Treatment duration (m)	9.00 (10.8)	7.50 (13.5)	11.5 (6.5)	0.677
Previous cirrhosis	23 (37.7%)	12 (30%)	11 (52.4%)	**0.032**
Risk factors for hematological malignancy				
Previous underlying hemopathy***	16 (26.2%)	9 (22.5%)	7 (33.3%)	0.376
Chemo- or radiotherapy	13 (21.0%)	9 (23%)	4 (19.0%)	1
Non-liver Transplantation	4 (6.5%)	3 (7.5%)	1 (6%)	1
Liver transplantation	13 (21.3%)	5 (12.5%)	8 (38.1%)	**0.045**
Time since transplant (y)	9 (5.0%)	10.8 (4.7)	6.0 (6.3)	0.604
For hepatocellular carcinoma	8 (13.1%)	4 (10.8%)	4 (19.0%)	0.576

Continuous variables are represented with their median and IQR in brackets. Binary variables are represented by their count and percentage in brackets. Fisher's test or Wilcoxon – test used. DAA = Direct Acting Agents, HM= hematological malignancy. d= days, y= years, m=month. * Age at time of HM diagnosis. **Defined as the time lapse between first specific treatment administration and diagnosis of HM, *** DAA+ group: Chronic lymphoid leukaemia or hyperlymphocytosis (n=2), plasmablastic lymphoma (n=1), chronic myelomonocytic leukaemia (n=1), multiple myeloma (n=1), myelofibrosis (n=1), AML in remission for at least 10 year with no recurrence during our study (n=1), DAA – group: Non Hodgkin lymphoma (n=3), multiple myeloma (n=2), AML (n=1, in remission for at least 10 years), myelofibrosis (n=1), myelodysplasia (n=2)

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

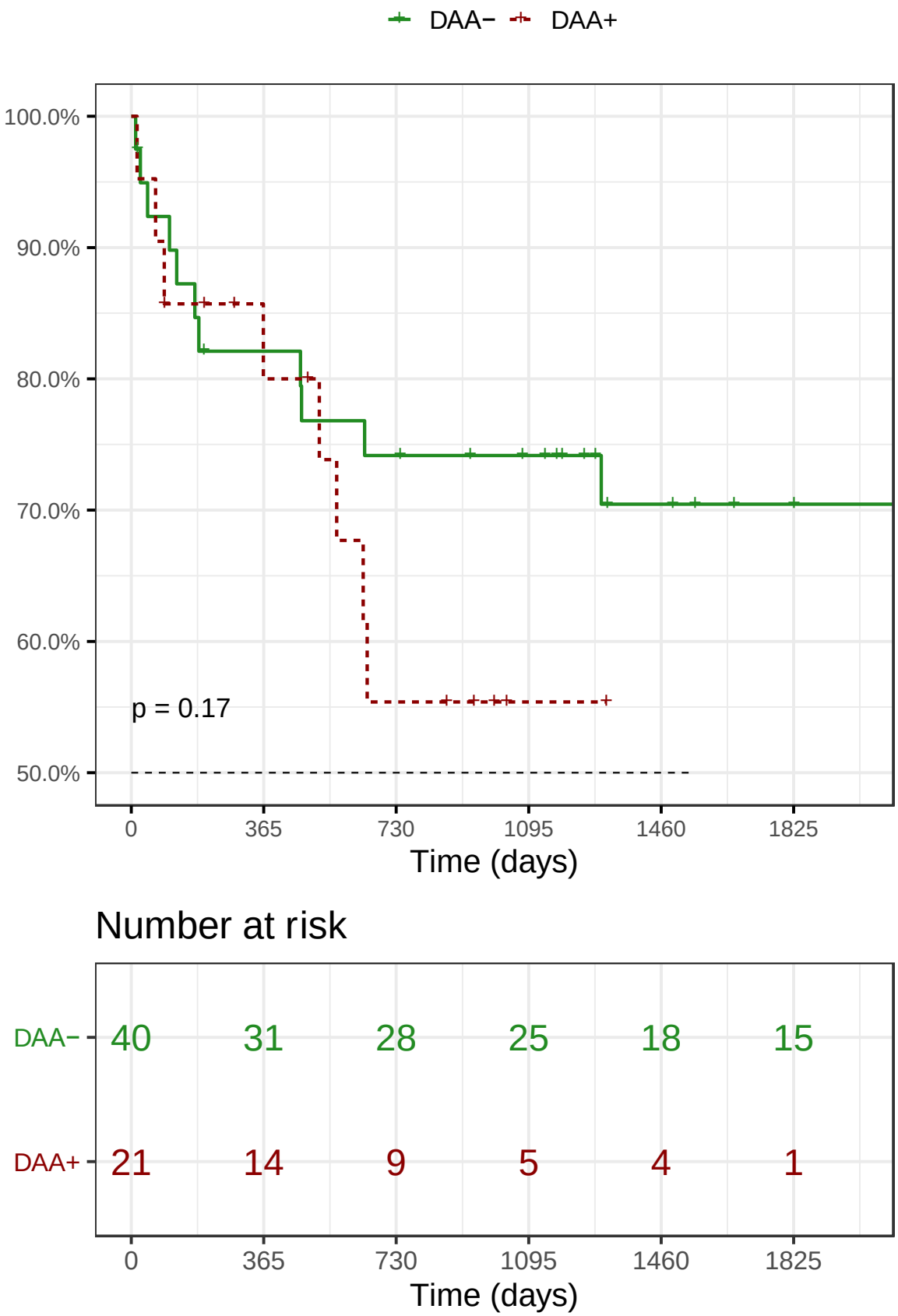
Part B

Hematological malignancy	Total (n=61)	Group DAA – (n = 40)	Group DAA+ (n = 21)	p-value
Lymphoid neoplasms				
Non-Hodgkin Lymphoma	28 (45.9%)	20 (50%)	8 (38.1 %)	0.427
Hodgkin's Lymphoma	5 (8.2%)	3 (7.5%)	2 (9.5%)	0.629
Chronic lymphocytic Leukaemia	1 (1.6%)	0 (0%)	1 (4.8%)	0.298
Plasma-cell disorders				
Multiple Myeloma	7 (11.5%)	5 (12.5%)	2 (9.5%)	1
AL Amyloidosis	1 (1.6%)	0 (0%)	1 (4.8%)	0.298
Myeloproliferative neoplasm	9 (14.8%)	7 (17.5%)	2 (9.5%)	0.479
Myelodysplastic syndrome	2 (3.3%)	2 (5%)	0 (0%)	1
Acute Leukaemia				
Acute lymphoblastic Leukaemia	1 (1.6%)	1 (2.5%)	0 (0%)	1
Acute myeloid Leukaemia	7 (11.5%)	2 (5%)	5 (23.8%)	**0.020**
Including mixed phenotype	2 (3.3%)	0 (0%)	2 (9.5%)	
Grouping MH				
Lymphoid neoplasms†	35 (57.4%)	24 (60.0%)	11 (52.4%)	0.866
Plasma-cell disorders††	18 (29.5%)	11 (27.5%)	7 (33.3%)	
Myeloid neoplasm†††	8 (13.1%)	5 (12.5%)	3 (14.3%)	
Outcome				
Follow up since HM diagnosis (m)	36 (48.3)	42.6 (70.6)	21.1 (24.8)	**0.024**
Bone marrow transplantation	6 (9.8%)	3 (7.5%)	3 (14.3%)	0.822
Death	21 (34.4%)	12 (30.0%)	9 (42.9%)	0.17*

Continuous variables are represented with their median and IQR in brackets. Binary variables are represented by their count and percentage in brackets. Fisher's test or Wilcoxon – test used. DAA = Direct Acting Agents, HM= hematological malignancy. d= days, y= years, m=month, * Cox test, † includes Non-hodgkin lymphoma, Hodgkin lymphoma, Chronic lymphocytic Leukaemia, ALL, †† includes Multiple myeloma, AL amyloidosis, ††† includes Myeloproliferative neoplasms, Myelodysplastic syndrome and AML

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Figure 2: Kaplan-Meyer Survival curve after onset of MH between the group DAA + (red) and



DAA – (green) using the Cox model

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Table 2: Characteristics of AML

			Risk factors				Malignant hemopathy					HCV					
Group	Year	Sex	Age	VIH	Previous MH	CtRt	Typ	GMT	FU	Metavir	Transplant	RBV	IFN	DAA lines	Last DAA treatment		
															Type	Duration (d)	Delay to diagnosis*
DAA-	2014	M	65	No	CLL	Yes	AML	No	Death	F0	No	Yes	Yes		None		
DAA-	2016	M	60	Yes	RAEB II	No	AML	No	Death	F4	No	No	No		None		
DAA+	2016	M	58	No	No	No	AML	No	Death	F4	No	No	No	1	SofDac	90	M-19
DAA+	2015	M	63	No	Myelofibrosis	Yes	AML	No	Death	F0	No	Yes	Yes	2	SofDac	80	M-30
DAA+	2015	F	79	No	Myelofibrosis	Yes	AML	No	Death	F3	No	Yes	Yes	1	SofSim	89	M-14
DAA+	2017	M	51	No	No	No	AML + T	Yes	Remission	F4	Yes	Yes	Yes	3	SofDac	180	M-72
DAA+	2016	F	48	No	No	No	AML +B	Yes	Death.	F1	Yes	No	No	1	SofLed	176	M-23

HM= Hematological malignancy , 2nd=secondary character, GMT =graft marrow transplantation, CtRt=Previous chemo – or radiotherapy, BMT =Bone marrow transplant, FU= Outcome, LT= liver transplant, RBV= exposure to ribavirin, IFN= exposure to interferon, *Delay to diagnosis= time between the beginning of DAA treatment and MH diagnosis, SofDac= Sofosbuvir+Daclatasvir, SofSim=Sofosbuvir+Simeprevir, Tel=Telaprevir, Led=Ledipasvir, RAEB II= Refractory anemia with excess blasts type II, AML=Acute myeloid Leukaemia, MPAL= Mixed phenotype acute Leukaemia

Table 3. Specific molecular characteristics of AML

Group	Precise Diagnosis	Caryotype	FLT3/NPM1	FISH	NGS mutations
DAA-	Therapy-related AML (t-AML)	47,XY,+1,der(1;7)(q10;p10),+8[13]/46,XY[7]	NA	del7q	NA
DAA-	AML-MRC	45,XY,-7[11]/46,XY[9]	NA	monosomy 7	NA
DAA+	AML with myelodysplasia-related changes (MRC)	46,XY,del(7)(q3?5)[8]/46,XY[12]	FLT3-/NPM1-	del7q	NA
DAA+	AML-MRC	48,XY,+12,+21[20]	FLT3-/NPM1-	tri12, tri21	ASXL1, GATA2, KRAS, PTPN11, SETBP1, SRSF2, STAG2
DAA+	AML, not otherwise specified (NOS)	46,XX[25]	NA	0	NA
DAA+	MPAL, T/myeloid, NOS	46,XY[20]	FLT3-ITD/NPM1-	0	0
DAA+	MPAL, B/myeloid, NOS	46,XX[20]	FLT3-ITD/NPM1-	0	FLT3-TKD, RUNX1

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

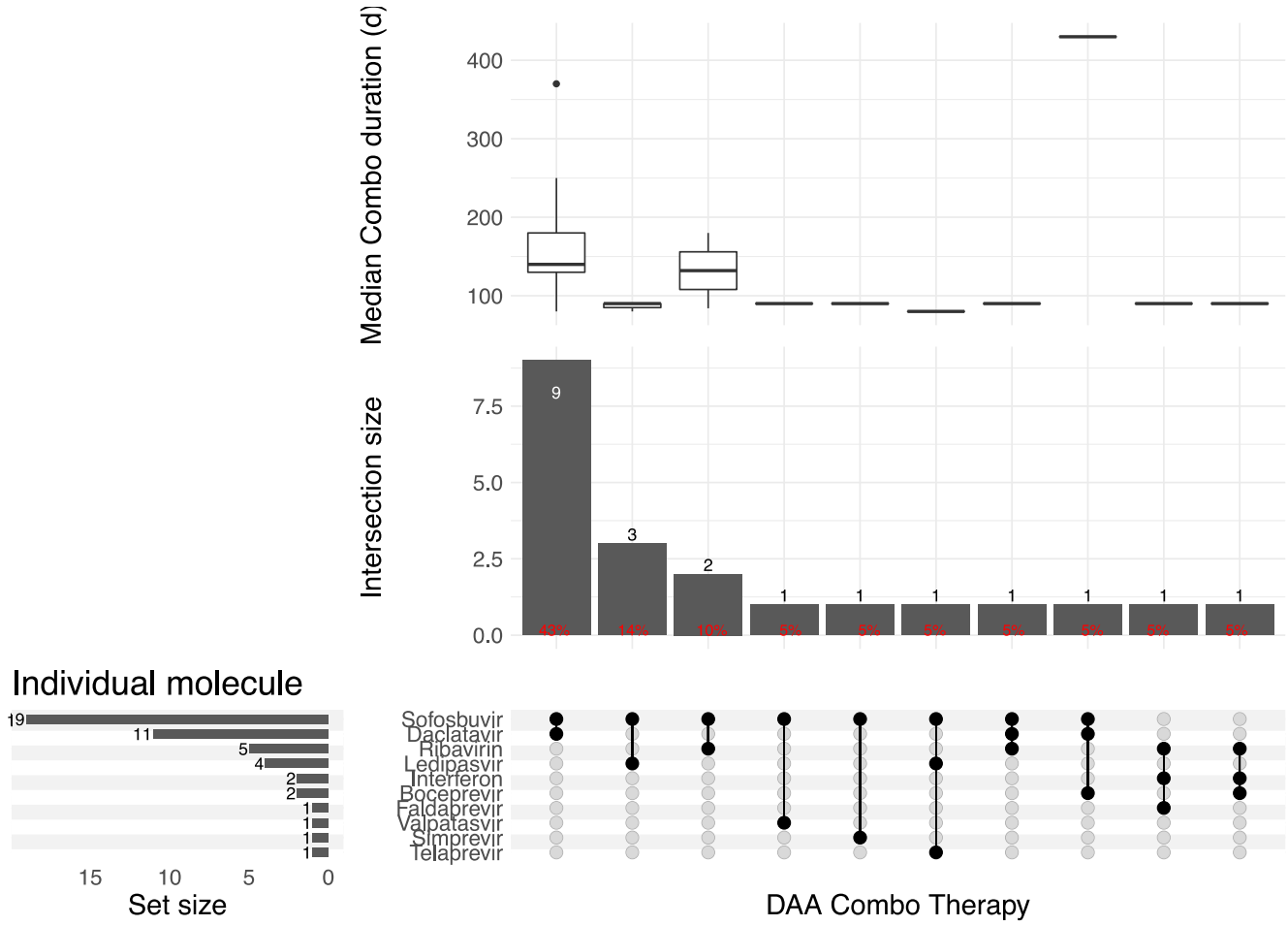
Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

Supplemental data 1: Detail of Non-inclusion criteria

Benign hematological disorder or no accurate hematologic diagnosis (n=49)	Anemia of various etiologies (n=6): deficiency (n=2), unknown (n=2), inflammatory (n=1), multifactorial (n=1) Benign cytopenia (n=6): Moderate thrombocytopenia (n=2), lymphopenia (n=1), neutropenia (n=1), cytopenia linked to a viral infection (n=2) Hemolytic anemia with various etiologies (n=4): mechanic (n=1), autoimmune (n=1), unknown (n=2) MGUS (n=5) Porphyria (n=1) Drug related cytopenia (n=3) Benign ethnic neutropenia (n=3) Hemoglobinopathies: thalassemia (n=3), sickle-cell anemia (n=3), other (n=1) Hemochromatosis or hyperferritinemia (n=3) Benign adenopathy (n=4) Secondary polycythemia (n=5) Bleeding disorder (n=1) Multifactorial pancytopenia (n=1)
Absence of chronic HCV infection at time of MH diagnosis (n=22)	Identical names (n=16) Negative HCV serology and viral load with birth dates in DAA list (n=2) Chart record error (n=1) Acute HCV infection (n=2) Seroconversion after hemopathy (n=1)
Hemopathy related to HCV or HCV treatment (n=14)	HCV induced cytopenia (n=4) Thrombocytopenia due to hepatopathy (n=4) Pancytopenia due to Peginterféron alfa-2a (n=1) Interferon linked Hematologic toxicity (n=2) Ribavirin linked hemolytic anemia (n=1) Bone marrow failure linked to protease inhibitor (n=2)
Cured malignant MH (n=13)	Including bone marrow transplanted patients
Other (n=5)	Absence of patient (n=1) Preventive Follow up (bone marrow transplant were the donor developed later chronic lymphoid Leukaemia, n=1) Inpatient care for family history of multiple hematologic malignancies (n=1) HIV follow up (n=2)

Abbreviations (in order of appearance): hepatitis C virus (HCV), hematological malignancies (HM), anti-HCV Direct Acting Antivirals (DAA), Acute Myeloid Leukaemia (AML), Non-Hodgkin Lymphoma (NHL), Mixed Phenotype Acute Leukaemia (MPAL)

<u>Supplemental data 2</u>: Last combined DAA effective therapy (n=21, group DAA +) The intersection size part represents the absolute number of combined therapy schemes and the lower part the absolute number per single molecule. Previous ligns when applicable are not represented.



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