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First real-life results on patients with advanced systemic mastocytosis treated with midostaurin in France

Background

Mastocytosis is a heterogeneous group of rare diseases related to the proliferation and/or abnormal accumulation of mast cells in one or more organs. The most common form, observed mostly in children, is cutaneous mastocytosis where the infiltration of mast cells is limited to the skin. When it reaches other organs, the disease is called systemic mastocytosis (SM). SM is frequently indolent with normal life expectancy but is life threatening in patients with advanced SM.

The 2016 WHO classification has 5 subtypes of systemic mastocytosis: Indolent Systemic Mastocytosis (ISM), Smoldering Systemic Mastocytosis (SSM), Aggressive Systemic Mastocytosis (ASM), Systemic Mastocytosis with an Associated Hematological Neoplasm (SM-AHN) and Mast Cell Leukemia (MCL).

In France, midostaurin, a tyrosine kinase inhibitor, is the only approved treatment for the three advanced SM subtypes [Aggressive Systemic Mastocytosis (ASM), Systemic Mastocytosis with Associated Haemotological Neoplasms (SM-AHN) and Mast Cell Leukemia (MCL)].

Objectives

Primary objective

To describe characteristics of patients treated by midostaurin in real-life between 2012 and 2018

Secondary objectives

To describe treatment history of patients treated with midostaurin between 2012 and 2018

To estimate midostaurin treatment duration between 2012 and 2018

To describe the adverse events of patients treated with midostaurin between 2012 and 2018

To estimate the overall survival of patients treated with midostaurin

Methods

Study overview

A retrospective cohort study was conducted using the French National Healthcare Database (Système National des Données de Santé - SNDS).

Data sources

The SNDS incorporates main French health public databases such as:

- SNIIRAM that records all reimbursed healthcare consumption in 2 databases:
  - DCIR with outpatient healthcare consumption data
  - PMSI with hospital healthcare consumption data
- CépiDC that records data on the medical causes of death

Study population

Inclusion criteria:

Adults (≥18 years old)

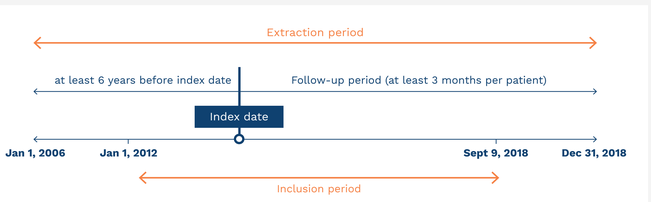
Patients with at least one midostaurin dispensing reimbursed between January 1, 2012 and September 30, 2018

Exclusion criteria:

Patients with non unique identifiers (twins, triplets, fictive Identifiers)

Patients with Acute Myeloid Leukemia (AML) without SM

Study period



Statistical analysis

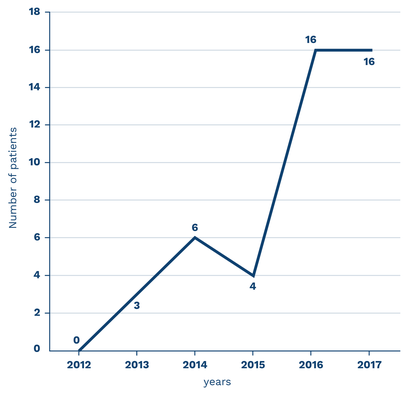
Kaplan Meier model was used to assess survival and competing risk survival model was used to assess treatment duration, using death as competing risk.

Survival analysis was realized on a sub-group of patients exclusively affiliated to the French general insurance scheme.

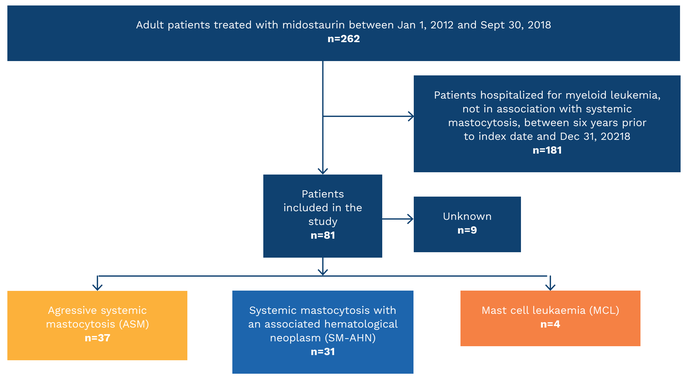
Results

Study population

Patients distribution over time



Patient disposition



Including 61 patients in the General Health Insurance scheme used for the survival analysis

Study population characteristics

Characteristics	All patients (**n=81**)	ASM (**n=37**)	SM-AHN (**n=31**)	MCL (**n=4**)
Age in years, mean (SD)	63.4 ±14.2	64.8 ±11.8	61.8 ±16.2	69.8 ±10.0
Sex	64.2% ♂ 35.8% ♀	70.3% ♂ 29.7% ♀	64.5% ♂ 35.5% ♀	50.0% ♂ 50.0% ♀
Time since diagnosis in months, mean (SD)	35.5 ±39.6	51.2 ±42.6	19.4 ±22.6	35.5 ±39.6

Comorbidities reported up to six years prior to index date, n (%)	All patients (**n=81**)	ASM (**n=37**)	SM-AHN (**n=31**)	MCL (**n=4**)
Associated hematological neoplasm	39.5%	0.0%	100.0%	25.0%
Osteoporosis	33.3%	46.0%	22.6%	0.0%
Liver disease, including cirrhosis	22.2%	24.3%	25.8%	25.0%
Cancer (former or on-going)	21.0%	18.9%	22.6%	0.0%
Heart disease	21.0%	18.9%	25.8%	50.0%
Diabetes	17.3%	18.9%	19.4%	25.0%
Bone fracture	14.2%	16.2%	16.1%	0.0%
Chronic end stage renal disease	0.0%	0.0%	0.0%	0.0%

Treatment, n (%)	All patients (**n=81**)	ASM (**n=37**)	SM-AHN (**n=31**)	MCL (**n=4**)
At least one of the below cytoreductive therapy	25.9%	27.0%	25.8%	25.0%
Cladribine	9.9%	13.5%	3.2%	25.0%
Chemotherapy: idarubicine, daunorubicine, cytarabine, brentuximab, azacitidine	8.6%	2.7%	19.4%	0.0%
Alpha interferon	7.4%	10.8%	0.0%	0.0%
Tyrosine kinase inhibitors: imatinib, dasatinib	3.7%	0.0%	6.5%	0.0%
Rapamycin (sirolimus), everolimus	1.2%	1.0%	0.0%	0.0%

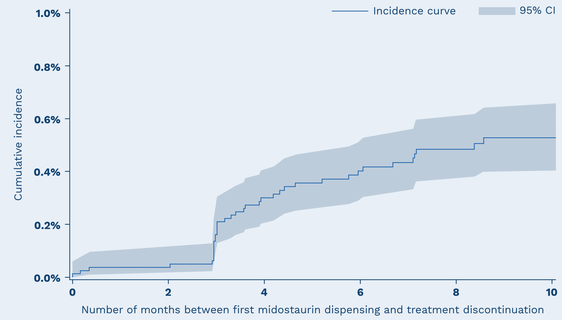
Serious adverse events	All patients (**n=81**)	ASM (**n=37**)	SM-AHN (**n=31**)	MCL (**n=4**)
Pneumonia	7.4%	5.4%	9.7%	25.0%
Dyspnea, pleural effusion	2.5%	2.7%	3.2%	0.0%
Nausea, vomiting, diarrhea	2.5%	2.7%	3.2%	0.0%
Sepsis	2.5%	0.0%	0.0%	50.0%
Gastrointestinal hemorrhage	0.0%	0.0%	0.0%	0.0%
Urinary tract infection	0.0%	0.0%	0.0%	0.0%
Febrile neutropenia	0.0%	0.0%	0.0%	0.0%
Photosensitization	0.0%	0.0%	0.0%	0.0%
Neurological disorders (memory, confusion)	0.0%	0.0%	0.0%	0.0%

Discontinuation

Discontinuation from the study was firstly due to a treatment discontinuation **(42%)** followed by the end of the study period (Dec 31, 2018, **35%**), death **(16%)** and switch to another treatment **(7%)**.

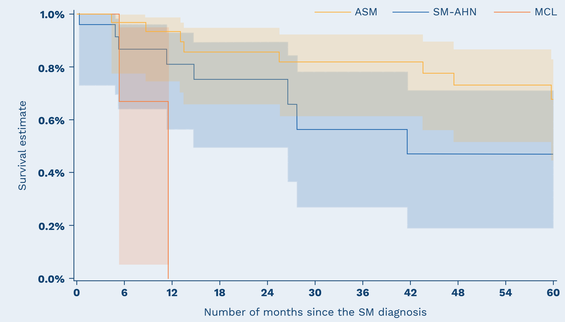
Midostaurin treatment duration

Median treatment duration was **8.4 months**.



Overall patient survival since AdvSM diagnosis, according to the subtype (n=61)

The estimated overall survival (considering any death) from time since diagnosis was 83% at one year and 56% at five years. The overall survival in the different AdvSM sub-types was statistically different (p=0.0095) with ASM>SM-AHN>MCL: 1-year overall survival was respectively 93% for ASM patients, 81% for SM-AHN patients and 0% for MCL patients.



Conclusion

This study described for the first time the characteristics and outcomes of patients treated in real-life with midostaurin for advanced SM in France.

It highlights that in routine clinical practice the characteristics of the patients, their disease management, treatment tolerance (treatment discontinuation) and survival were in line with previous published results (compassionate use and clinical trials).

This study confirms the positive outcomes of midostaurin in advanced SM patients in France.

SNIIRAM study registered with the INDS on Sep 5, 2019 and authorised by the CNIL on Nov 20, 2019. (DR-2019-363 (request 919345v1)) - CNAM agreement signed on Feb 5, 2020