Survival of patients with advanced hepatocellular carcinoma treated with sorafenib in France over the period 2009-2018: analysis of the French hospital and claim database

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INTRODUCTION

The incidence of primary liver cancer increased significantly in France over the recent years. A national estimate of 10,580 new cases of primary liver cancer was given in 2018 for metropolitan France (1). Hepatocellular carcinoma (HCC) represented approximately 90% of cases (2). HCC often diagnosed at an advanced stage had a very poor prognosis. HCC is currently the fourth leading cause of cancer-related death globally (3). Since 2007, sorafenib was the only first-line systemic therapy indicated in this indication.

AIM

The aim of this analysis was to describe the profile, risk factors, overall survival (OS) and Time To treatment Discontinuation (TTD) in patients with advanced HCC newly treated with sorafenib in France over the period 2009-2018.

METHOD

STUDY DESIGN

This study was conducted using the French nation-wide healthcare claims database (SNDS) which includes all items of reimbursed ambulatory and hospital care in more than 99% of the French population (nearly 66 million persons).

POPULATION

Patients treated with sorafenib for HCC were identified by the ICD-10 code C220 as a cause for Long-Term Disease (LTD) or as a diagnosis of hospitalization between 2009 and 2018.

ETIOLOGIES OF LIVER DISEASE

The etiologies of the underlying chronic liver disease (CLD) were identified from ICD-10 codes and ATC codes of specific treatments.

STATISTICAL ANALYSIS

OS was defined from sorafenib initiation (index date) until death or last follow-up visit for those still alive at the end of study period. TTD was defined as the time from sorafenib initiation until treatment discontinuation, death or censored at last follow-up .

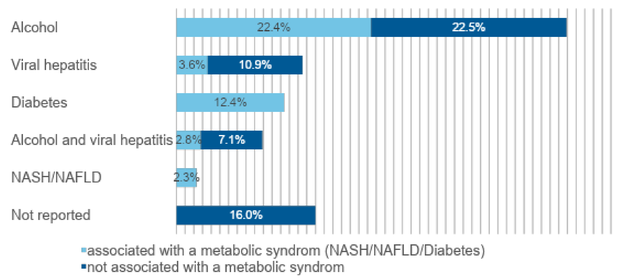
The Kaplan-Meier method was used to estimate survival rates. A cox modelling multivariate analysis has been performed to adjust the results on confounding factors.

RESULTS

17,680 newly treated with sorafenib HCC patients were identified. Their mean age was 66.9 years (SD:10.3) and 87.6% were male. The most frequent cause of underlying CLD were alcohol liver disease (54.8%) and viral hepatitis (24.4%).

Alcoholic and / or viral hepatitis alone or in combination were prioritized to define the main etiology of interest (Figure 1).

Figure 1: Etiology of HCC (only one response after ranking)



The median OS from sorafenib initiation was 8.4 months (95%CI [8.2; 8.7]). OS appeared similar whatever the etiologies except in patients with hepatitis B (Table 2).

Figure 2: OS according to HCC etiology

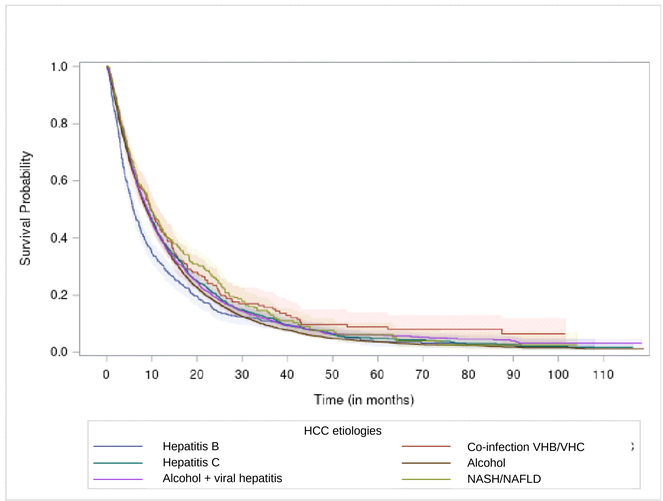


Table 1: Sociodemographic characteristics and hepatic etiologies of patients treated with sorafenib

HCC **Population**	17,680 (100%)
Gender, Male N (%)	15,480 (87.6%)
Age (years) at sorafenib initiation	
Mean (Standard deviation)	66.9 (10.3)
Median / Min / Max	68.0 / 10.0 / 94.0
Quartile 25 / Quartile 75	61.0 / 74.0
HCC etiologies (several etiologies possible)	
Viral Hepatitis B	1,299 (7.3%)
Viral Hepatitis C	3,459 (19.6%)
Alcohol	9,682 (54.8%)
NASH/NAFLD	1,246 (7.0%)
Diabetes	7,564 (42.8%)
Not reported	2,829 (16.0%)

Table 2: Median OS according to HCC etiology

HCC **Etiology**	17,680* (100%)	Median OS (months) 95%CI
Alcohol + viral hepatitis	1,749 (9.9%)	8.9 [8.4 – 9.6]
Alcohol	7,933 (44.9%)	8.8 [8.4 – 9.1]
Hepatitis B	655 (3.7%)	5.9 [5.3 – 6.9]
Hepatitis C	1,646 (9.3%)	9.0 [8.2 – 9.7]
Co-infection VHB/VHC	268 (1.5%)	9.7 [8.2 – 11.7]
NASH/NAFLD	403 (2.3%)	9.8 [8.9 – 11.8]

**5,026 have not recorded etiology in database: 43.7% of these patients have diabetes*

Figure 3: Median OS according to the calendar year of sorafenib initiation

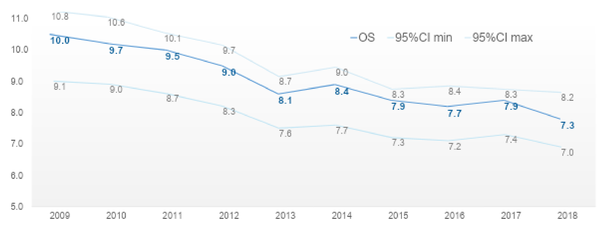
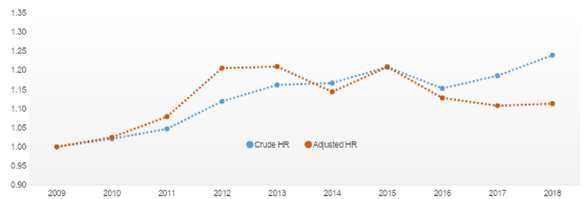


Figure 4: Results of the multivariate cox model (*) on mortality according to the calendar year of sorafenib initiation (HR taking 2009 as reference)



(*) adjustment variables: age, gender, etiology, other comorbidity, curative treatment, TACE, TARE, delay between, HCC diagnosis and initiation of sorafenib

The median survival decreased over the period: from 10.0 months in 2009 to 7.3 months in 2018. However, after adjustment on patient's profile and clinical characteristics this increase in mortality rate still only until 2012. After, OS appears stable over the time.

The median TTD was 3.5 months (95%CI: 3.3-3.7); only 15.0% of patients were still treated in first line at 12 months.

DISCUSSION

This study, based on the SNDS, covers all subjects treated in France with sorafenib and therefore does not include sampling bias. However, this database has the same limitations as all the health claims systems. It does not contain all socio-economic data or all clinical data, so does not provide any exhaustive information on risk factors. Consequently, the proportion of alcoholic etiology and NASH/NAFLD had probably been underestimated in this study.

The OS is lower than in clinical trials. This difference is probably related to the selection of individuals with a better prognosis in trials than in real-world sorafenib-treated population. The OS median survival decreased on the studied period between 2009 and 2018. The cause for this result could be due to a more serious treated patients and a more delayed initiation of sorafenib in recent years.

CONCLUSION

These results confirmed the high clinical burden of treated HCC regardless of the cause of CLD: OS in this real-world setting study is lower than in clinical trials.
The management of HCC at an earlier stage as well as the arrival of new treatments such as immunotherapy, will improve the prognosis of patients.

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