Treatment Patterns and Health Resource Utilization in Patients with Hepatocellular Cancer (HCC) Following Failure of Sorafenib in Real World Setting in Taiwan

Diego Novick[1], Narayan Rajan[2], Alice Wei[3], Rebecca Cheng[3], Agota Szende[4], Rebecca Baik[5], Sam Colman[6]

[1]Eli Lilly and Company, Surrey, United Kingdom; [2]Eli Lilly and Company, West Ryde, Australia; [3]Eli Lilly and Company, Taipei, Taiwan;

[4]Covance Market Access Services, Leeds, United Kingdom; [5]Covance Market Access Services, Gaithersburg, United States; [6]Covance Market Access Services, Sydney, Australia.

Introduction

- Eastern Asia experiences the highest incidence and mortality of liver cancer worldwide [1]. Hepatocellular carcinoma (HCC) accounts for approximately 90% of all liver cancer cases in Eastern Asia and 88% in Taiwan [2, 3].
- While the age-standardized incidence is decreasing slightly [4, 5], liver cancer remains the second highest cause of cancer mortality in Taiwan (8,258 deaths in 2015, crude rate 39.3 per 100,000, adjusted rate 22.5 per 100,000) [3].
- European, US, Asian and Taiwanese treatment guidelines all recommend sorafenib as first-line systemic therapy [6, 2, 7-9]. Taiwanese guidelines note that there is no strong evidence for cytotoxic chemotherapy following sorafenib. At the same time, several promising new treatments are emerging.
- The purpose of this study was to understand the current treatment patterns and health resource utilization (HRU) following the failure of sorafenib in patients with HCC living in Taiwan.

Patients and methods

- A chart review was conducted in 130 patients meeting the inclusion criteria of: ≥ 20 years old with HCC who received systemic therapy or best supportive care following failure of first-line systemic treatment with sorafenib between 2016 and 2018.
- Anonymized data on patient characteristics, treatment pathways and survival was abstracted by 30 physicians in Taiwan.
- Oncologists were asked to identify eligible patients from those meeting the inclusion/exclusion criteria, based on a randomly generated month of birth to avoid selection bias, and review those patients' charts to report anonymized patient-level information.
- The data abstraction form included questions on each subject's demographic characteristics, cancer directed treatments, supportive care treatments, and HRU.
- The index event was defined as the date of completion of sorafenib therapy. Information prior to the index event (pre period) was from the date of initial diagnosis of HCC. The observation period for each patient was from diagnosis date until date of data abstraction or death, whichever occurred earlier.
- This was a non-comparative study; however, the study objectives were assessed separately for patients with low alpha-fetoprotein (AFP < 400ng/mL) and high alpha-fetoprotein (AFP ≥400ng/mL), as tested at the commencement of second-line therapy or best supportive care post-sorafenib.
- Descriptive statistics were used to characterize the sample and treatment pathways overall and within AFP patient groups. Rates and 95% confidence intervals (CI) for HRU were evaluated using Poisson models, which included an offset of patient follow-up time. Progression-free survival (PFS) and overall survival (OS), were assessed using Kaplan-Meier methods.

Results

Physician Sample Characteristics

- Of the 30 physicians who provided patient data, 18 (60%) were medical oncologists and 12 (40%) were hepatologists. The majority of physicians were based at regional hospitals (53%) or academic medical centres (43%) with the remainder from district hospital. Physicians were located in the north (53%), south (27%), center (13%), and east (7%) of Taiwan.
- The median (IQR) time physicians had been practicing in HCC was 15 (10–18) years, and they reported currently treating a median (IQR) of 14 (8–30) patients per month.

Patient Sample Characteristics

- The mean (SD) age of the 130 patients was 61 (11.0) years at data abstraction and ranged from 27 to 84 years. The majority of patients were male (79%). Based on vital status reported at data collection, 78% of patients were deceased.
- At the time of HCC diagnosis the mUICC Stage was evenly spread, ranging from 14% with Stage IV B to 23% with Stage III A. The majority of patients had a BCLC Stage of C (46%) or B (31%), and Child Pugh class of A (89%).
- At time of post-sorafenib therapy, 65 (52%) patients had an ECOG score of 1, 57% and 68% had extrahepatic spread and macrovascular invasion, respectively. Among patients with extrahepatic spread the main organs involved included the lungs (57%), lymph nodes (46%), and bones (34%).
- A total of 81 (62%) patients had AFP ≥ 400ng/mL at time of post-sorafenib therapy, compared to 49 (38%) with AFP < 400ng/mL. The high AFP group was almost 5 years younger, slightly more likely to be deceased, had a higher mUICC and BCLC stage at HCC diagnosis, and a higher ECOG score at time of post-sorafenib therapy. The mean AFP level increased from 4,180 ng/mL at the time of HCC diagnosis to 5,692 ng/mL at commencement of post-sorafenib treatment.

Table 1: Patient characteristics

Characteristics	Total (N=130)	AFP <400 ng/mL (N=49)	AFP ≥400 ng/mL (N=81)
Age (years)[a]			
Mean (SD)	61.7 (11.01)	65.1 (10.03)	59.6 (11.12)
Range	27–84	43–84	27–79
Other characteristics, n (%)			
Male	103 (79.2)	38 (77.6)	65 (80.2)
Vital status: deceased at time of data abstraction	96 (78.0)	33 (75.0)	63 (79.7)
Not employed (student, retired, other)	87 (71.9)	32 (69.6)	55 (73.3)
HCC etiology, n (%)			
Hepatitis B virus [HBV]	91 (70.5)	33 (68.8)	58 (71.6)
Hepatitis C virus [HCV]	39 (30.2)	19 (39.6)	20 (24.7)
Alcohol use	27 (20.9)	11 (22.9)	16 (19.8)
Non-alcoholic fatty liver disease	3 (2.3)	0 (0.0)	3 (3.7)
Other	5 (3.9)	1 (2.1)	4 (4.9)
Do not know	1	1	0
mUICC stage at HCC diagnosis[b], n (%)			
Stage II	26 (21.8)	12 (28.6)	14 (18.2)
Stage III A	27 (22.7)	9 (21.4)	18 (23.4)
Stage III B	22 (18.5)	7 (16.7)	15 (19.5)
Stage IV A	21 (17.6)	7 (16.7)	14 (18.2)
Stage IV B	17 (14.3)	6 (14.3)	11 (14.3)
Barcelona Clinic Liver Cancer at HCC diagnosis, n (%)			
0	3 (2.4)	3 (6.1)	0 (0.0)
A	24 (18.9)	12 (24.5)	12 (15.4)
B	39 (30.7)	15 (30.6)	24 (30.8)
C	59 (46.5)	19 (38.8)	40 (51.3)
D	2 (1.6)	0 (0.0)	2 (2.6)
Do not know	3	0	3

Table 1: Patient characteristics (continued)

Characteristics	Total (N=130)	AFP <400 ng/mL (N=49)	AFP ≥400 ng/mL (N=81)
Child Pugh class at HCC diagnosis, n (%)			
A	116 (89.2)	44 (89.8)	72 (88.9)
B	14 (10.8)	5 (10.2)	9 (11.1)
AFP level at HCC diagnosis (ng/mL), mean (SD)	4180.0 (16162.61)	153.3 (254.62)	6677.6 (20218.62)
At time of commencement of second-line therapy or best supportive care post-sorafenib			
ECOG PS score, n (%)			
0	23 (18.5)	13 (28.3)	10 (12.8)
1	65 (52.4)	21 (45.7)	44 (56.4)
2+	36 (29.0)	12 (26.1)	24 (30.8)
Prognostic factors[c], n (%)			
Extrahepatic spread	67 (56.8)	21 (51.2)	46 (59.7)
Macrovascular invasion	80 (67.8)	27 (65.9)	53 (68.8)
Organs involved[b,c,d], n (%)			
Bone	23 (34.3)	7 (33.3)	16 (34.8)
Lung	38 (56.7)	8 (38.1)	30 (65.2)
Lymph node	31 (46.3)	14 (66.7)	17 (37.0)
Peritoneum	12 (17.9)	5 (23.8)	7 (15.2)
Liver function biomarkers			
AFP level (ng/mL), mean (SD)	5691.6 (16414.31)	133.2 (128.94)	9054.1 (20101.59)
Bilirubin (mg/dL), mean (SD)	1.69 (0.944)	1.67 (1.212)	1.70 (0.751)
Serum albumin (g/dL). mean (SD)	3.28 (0.516)	3.35 (0.531)	3.24 (0.506)
INR, mean (SD)	1.25 (0.277)	1.23 (0.273)	1.26 (0.280)

AFP, alpha-fetoprotein; ECOG, Eastern Cooperation Oncology Group; HCC, hepatocellular cancer; PS, performance status; INR, international normalized ratio; n, number of subjects; SD, standard deviation.
a Patient age at date of data abstraction, or for deceased patients: age at death.
b Only the categories which cover the majority of the patients are presented.
c Percentages may add to more than 100% as patients may be counted in more than one category.
d Among those with extrahepatic spread.

HCC Systemic Treatment Patterns

- The median (IQR) time from HCC diagnosis to sorafenib treatment was 6 (2–45) weeks, and the median (IQR) duration of sorafenib treatment was 18 (11–28) weeks. The main reason for sorafenib treatment discontinuation was disease progression (85%).
- For the high AFP group the median time to from HCC diagnosis to sorafenib treatment was shorter than for the low AFP group, 4 weeks vs. 7 weeks, respectively.
- Post-sorafenib, 60 (46%) patients had systemic therapy. Nivolumab monotherapy was the most common second line therapy used by 42% of patients. Regorafenib monotherapy and chemotherapy were the other main therapies used by 27% and 25% of patients, respectively.
- The most common reasons for systemic therapy selection post-sorafenib were: good performance status (60%), well preserved liver function (60%), and extent of macrovascular invasion/extent of metastatic disease (40%). The main reasons for discontinuation of second-line therapy were disease progression (65%), toxicity/adverse event (15%), or patient and/or clinician decision (15%).
- Nivolumab monotherapy was the most common third-line therapy, used by 50% of patients among the 16 patients who commenced third-line systemic therapy. Chemotherapy and regorafenib monotherapy were the other main therapies used by 25% and 19% of patients, respectively.
- There was a tendency of higher post-sorafenib chemotherapy use among the high AFP group compared to the low AFP group.

Table 2: HCC systemic treatment patterns post-sorafenib

Treatment	Total	AFP <400 ng/mL	AFP ≥400 ng/mL
Second-line therapy post-sorafenib, n (%)	(N=60)	(N=38)	(N=22)
Nivolumab monotherapy	25 (41.7)	9 (40.9)	16 (42.1)
Regorafenib monotherapy	16 (26.7)	9 (40.9)	7 (18.4)
Chemotherapy mono or combination	15 (25.0)	3 (13.6)	12 (31.6)
Reasons for selecting second-line therapy[a], n (%)			
Well preserved liver function	36 (60.0)	12 (54.5)	24 (63.2)
Good performance status	36 (60.0)	15 (68.2)	21 (55.3)
Extent of macrovascular invasion/extent of metastatic disease	24 (40.0)	11 (50.0)	13 (34.2)
Reasons for discontinuation of second-line therapy[a], n (%)			
Disease progression	39 (65.0)	11 (50.0)	28 (73.7)
Toxicity or adverse effect	9 (15.0)	5 (22.7)	4 (10.5)
Patient and/or clinician decision	9 (15.0)	3 (13.6)	6 (15.8)
Death	7 (11.7)	4 (18.2)	3 (7.9)
Third-line therapy post-sorafenib, n (%)	(N=16)	(N=6)	(N=10)
Nivolumab monotherapy	8 (50.0)	3 (50.0)	5 (50.0)
Chemotherapy mono or combination	4 (25.0)	0 (0.0)	4 (40.0)
Regorafenib monotherapy	3 (18.8)	3 (50.0)	0 (0.0)
Reasons for selecting third-line therapy[a], n (%)			
Well preserved liver function	10 (62.5)	3 (50.0)	7 (70.0)
Good performance status	8 (50.0)	3 (50.0)	5 (50.0)
Extent of macrovascular invasion/extent of metastatic disease	6 (37.5)	5 (83.3)	1 (10.0)
Reasons for discontinuation of third-line therapy[a], n (%)			
Disease progression	8 (50.0)	2 (33.3)	6 (60.0)
Death	4 (25.0)	3 (50.0)	1 (10.0)
Toxicity or adverse effect	2 (12.5)	1 (16.7)	1 (10.0)
Ongoing at time of data abstraction	3 (18.8)	2 (33.3)	1 (10.0)

AFP, alpha-fetoprotein; n, number of subjects.
[a]Only the categories with >15% patients are included. Percentages may add to more than 100% as patients may be counted in more than one category.

Adverse Events

- The most common grade 3 or higher adverse events during second-line therapy were asthenia/fatigue (53%) and ALT increase (40%).
- A total of 17 (28%) of patients did not experience any of the pre-specified severe adverse events during second-line therapy, including amylase increase, anaemia, colitis, diarrhea, fatigue/asthenia, hand-foot skin reaction, hepatitis, hyperkalemia, hypertension, hyperthyroidism, hyponatremia, hypothyroidism, increased alkaline phosphatase, increased alanine aminotransferase (AST), increased aspartate aminotransferase (ALT), internal bleeding, lipase increase, nephritis, pneumonitis, renal dysfunction, and thrombocytopenia.

Health Care Resource Utilization

- HRU included: oncologists, hepatologists and gastroenterologist visits, at an average rate of 7.4 (95% CI: 6.9, 8.1), 3.2 (95% CI: 2.8, 3.6) and 3.0 (95% CI: 2.6, 3.4) visits per person-year, respectively, and hospitalizations, with a rate of 2.2 (95% CI: 1.9, 2.6) per year per patient, and a mean (SD) length of stay of 10.6 (11.46) days.
- HRU was generally greater in the high AFP group compared to the low AFP group.

Table 3: Health care resource utilization after diagnosis of HCC

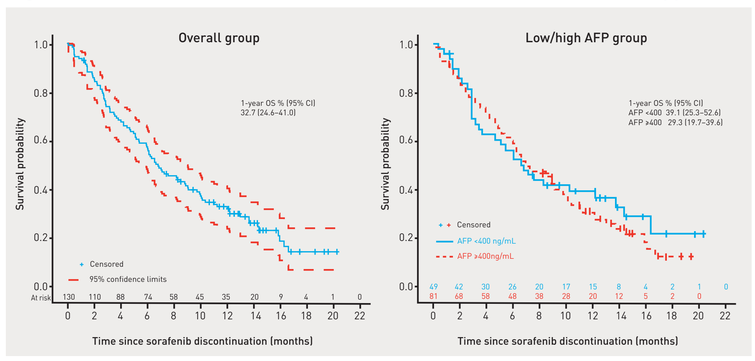
	Total (N=130)	AFP <400 ng/mL (N=49)	AFP ≥400 ng/mL (N=81)
	Annual rate (95% CI)[a]		
Diagnostic and monitoring tests			
Tumor markers	4.77 (4.32, 5.26)	3.88 (3.24, 4.65)	5.28 (4.69, 5.95)
Ultrasound	3.69 (3.29, 4.13)	3.83 (3.18, 4.62)	3.61 (3.13, 4.16)
CT	3.45 (3.08, 3.88)	3.52 (2.92, 4.25)	3.41 (2.95, 3.95)
Chest X-ray	2.90 (2.56, 3.29)	2.41 (1.92, 3.02)	3.20 (2.75, 3.73)
MRI	0.63 (0.48, 0.83)	0.32 (0.17, 0.60)	0.82 (0.61, 1.11)
Bone scan	0.57 (0.43, 0.76)	0.39 (0.22, 0.68)	0.69 (0.50, 0.95)
Office visits			
Oncologist	7.44 (6.86, 8.06)	6.29 (5.47, 7.24)	8.16 (7.40, 9.00)
Hepatologist	3.19 (2.82, 3.59)	3.44 (2.84, 4.15)	3.04 (2.60, 3.55)
Gastroenterologist	2.99 (2.64, 3.40)	3.18 (2.61, 3.87)	2.88 (2.44, 3.39)
Blood transfusion	4.76 (4.31, 5.26)	4.78 (4.07, 5.62)	4.75 (4.17, 5.40)
Accident and emergency visits	1.39 (1.16, 1.67)	1.22 (0.89, 1.68)	1.49 (1.19, 1.86)
Hospitalization	2.23 (1.93, 2.57)	1.73 (1.33, 2.26)	2.52 (2.13, 2.99)
Length of stay per hospitalization (days, SD)	10.6 (11.46)	8.5 (4.43)	11.6 (13.40)

AFP, alpha-fetoprotein; CI, confidence interval; CT, computed tomography; HCC, hepatocellular cancer; MRI, magnetic resonance imaging; n, number of subjects, SD, standard deviation.
a Rates are per person and per year with Poisson 95% CIs.

Survival

- The OS from discontinuation of sorafenib treatment at 1 year was 39% (95% CI: 25%–53%) and 29% (95% CI: 20%–40%) in the low and high AFP groups, respectively. However, the median OS was 6.9 months (95% CI: 5.9, 9.0) overall and similar between the AFP groups: 6.8 months (95% CI: 3.5, 13.6) and 7.0 months (95% CI: 5.4, 9.7) in the low and high AFP groups, respectively.

Figure 1: Overall survival since commencement of second-line therapy



Discussion

- This study presents an up-to-date overview of current treatment pathways and HRU in patients with HCC who received systemic therapy or best supportive care following failure of first-line systemic treatment with sorafenib in the real world setting in Taiwan.
- The findings showed that nivolumab monotherapy was used by nearly half of the patients post first-line sorafenib, despite Asian and European guidelines not currently recommending nivolumab. Evidence on effectiveness of immune checkpoint inhibitors single agent is currently lacking.
- Chemotherapy was used by approximately a quarter of patients post first-line sorafenib, which the 2016 Taiwanese guidelines indicated would be useful for patients with advanced tumors with good performance status and well-preserved liver function.
- HRU data indicated high utilization of hepatologist and oncologist visits, as well as a high rate of and duration of hospitalization among all patients, particularly in the high AFP group.
- OS across all patients in the chart review sample (6.9 months) was also comparable with OS reported in several other HCC clinical trials, such as the RESORCE [10] and CELESTIAL [11] that reported OS between 7.8 months and 10.2 months across trials and their treatment groups.
- Some limitations of this study need to be highlighted. While the sample had a good representation of geographic areas and types of hospitals within Taiwan, generalizability of results to other countries may be limited. In addition, there have been changes in available registered and reimbursed medications since the data collection of this study that may impact future prescription patterns. Namely, lenvatinib has been approved for first-line treatment, while both lenvatinib and regorafenib got reimbursement status in June 2019 and January 2020, respectively, in Taiwan.
- This real world evidence research highlighted continuing high mortality in HCC, underlying a need for new treatments that can lengthen survival. Results can inform future evaluations of new HCC treatments that estimate the health economic impact of their adoption in Taiwan.

References

1. Ferlay J, Ervik M, et al. Global Cancer Observatory: Cancer Today. 2018. Retrieved 8 Oct 2018, from https://gco.iarc.fr/today. 2. EASL. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182-236. 3.Ministry of Health and Welfare. 104 Cancer Registry Annual Report (2015). 2017. Retrieved 31 May 2018, from https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=8084. 4.Chiang CJ, Lo WC, Yang YW, et al. Incidence and survival of adult cancer patients in Taiwan, 2002-2012. J Formos Med Assoc. 2016 Dec;115(12):1076-88. 5.Taiwan Cancer Registry. Top 10 cancers in Taiwan 2008-2014. 2016. Retrieved 29 May 2018, from http://tcr.cph.ntu.edu.tw/uploadimages/Top%2010%20cancer%20in%20Taiwan%202008-2014.pdf. 6.Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017 Jul;11(4):317-70. 7. Surveillance group, Diagnosis group, Staging group et al. Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. J Formos Med Assoc. 2018 May;117(5):381-403. 8. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723-50. 9. NCCN. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. Version 3.2018 - August 29, 2018. 2018. Retrieved 28 Sep 2018, from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 10. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66. 11. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018 Jul 5;379(1):54-63.