Treatment sequencing options in advanced hepatocellular carcinoma: preliminary data from a single-center retrospective cohort

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INTRODUCTION

- The treatment scenario of advanced HCC (aHCC) has been widened by the availability of new tyrosine-kinase inhibitors (TKI) [1-3], antiangiogenics [4,5] and immuno-oncological (IO) drugs [5,6].
- Today a sequential strategy is possible; however, how to individualize first and further lines' options is still unclear.

AIM

Our aim is to describe and compare progression-free (PFS) and overall survival (OS) of sequential systemic treatments in aHCC.

METHOD

- We retrospectively collected data from aHCC patients treated at our Institution from January 2010 to January 2020.
- We defined:
  - PFS1 and PFS2 as the time from first-line (1L) and second-line (2L) beginning, respectively, to progressive disease (PD);
  - PFS1+2 as the time from 1L start to PD at 2L;
  - OS2 as the time from 2L beginning to death.
- Kaplan-Meier method and Cox regression model were used.

RESULTS

- Among 77 enrolled patients: **in 1L**, 68 patients (88.3%) received sorafenib (Sor) and 9 (11.7%) IO, with an mPFS1 of 8.2 vs 3.1 mo (p=0.005) and mOS of 26.3 vs 15.7 mo (p=0.12), respectively; **in 2L**, among patients treated with Sor, 28 (41.2%) received TKI (25 regorafenib, 3 cabozantinib), 34 (50.0%) CT (capecitabine and/or cyclophosphamide) and 6 (8.8%) IO (anti-PD1 agents), while all patients treated with IO received Sor as 2L.
- **4 sequential approaches** were identified: A**) Sor-TKI**, B) **Sor-CT**, C) **Sor-IO**, D) **IO-Sor**, reporting an mPFS1+2 of 17.2 (A), 10.0 (B), 14.2 (C) and 7.8 (D) mo (p=0.008), and mOS of 26.3 (A), 19.8 (B), 22.6 (C) and 15.7 (D) mo (p=0.34).
- mPFS2 didn't seem to be influenced by mPFS1, neither in Sor nor in IO-starting sequences (all p>0.05).
- A better OS2 was reported in who achieved a PFS1 longer than median value, with a statistically significance in Sor group (10.4 vs 5.7 mo, p=0.03) and a trend in IO one (8.5 vs 7.7 mo, p=0.067).
- Uni- and multivariate survival correlations with baseline features were run for all sequences; Sor-TKI and IO-Sor univariate data were detailed in **Table1.**

	Sorafenib→ TKI				IO → Sorafenib			
	mPFS1+2		mOS		mPFS1+2		mOS	
	n	months (95% CI)	n	months (95% CI)	n	months (95% CI)	n	months (95% CI)
Overall, months (95% CI)	28	17.2 (12.6 - 21.8)	28	26.3 (19.2 - 41.2)	9	7.7 (5.4 - 10.7)	9	15.7 (10.7 - 19.9)
AFP								
>400	3	4.1 (3.3 - 21.1)	3	20.7 (7.9 - 20.7)	4	6.4 (4.7 - 13.3)	4	10.7 (6.6 - 15.7)
<400	16	21.8 (13.4 - 26.1)	16	29.6 (19.2 - 32.3)	5	10.5 (5.1 - 11.9)	5	19.9 (10.7 - ND)
		p=0.015		p=0.25		P=0.866		P=0.83
ECOG PS								
0	19	15.4 (12.6 - 21.8)	19	26.3 (17.2 - 41.2)	8	7.8 (5.4 - 11.9)	8	15.7 (10.7 - 19.9)
1	9	21.2 (6.3 - 21.9)	9	30.9 (20.7 - 32.3)	1	4.7 (ND)	1	10.7 (ND)
		P=0.77		P=0.65				P=0.28
BCLC score								
B	11	21.1 (14.8 - 21.8)	11	29.6 (26.3 - 66.4)	3	10.7 (7.8 - 13.3)	3	15.7 (15.7 - 15.7)
C	17	13.4 (8.6 - 21.8)	17	20.7 (17.2 - 32.3)	6	5.4 (5.1 - 10.5)	6	10.7 (10.7 - 19.9)
		P=0.70		P=0.27		P=0.17		P=0.13
Etiology								
HCV infection	10	21.1 (17.2 - 21.9)	10	29.6 (26.3 - 66.4)	1	11.9 (ND)	1	19.9 (ND)
HBV infection	5	12.0 (6.3 - 21.8)	5	12.1 (7.4 - 41.2)	2	5.1 (5.1 - 5.4)	2	10.7 (10.7 - 12.1)
HCV+HBV	3	11.7 (6.1 - 14.8)	3	17.2 (17.2 - 17.8)	-	-	-	-
Alcohol+dismet	7	21.2 (21.2 - 26.1)	7	30.9 (ND)	2	4.7 (4.7 - 10.7)	2	10.7 (10.7 - 10.7)
Other	3	4.1 (3.3 - 15.4)	3	20.7 (8.0 - 26.3)	4	7.8 (6.1 - 13.3)	4	15.7 (6.6 - 15.7)
		P=0.0081		P=0.24		P=0.19		P=0.44
Extent of disease								
Liver only	16	21.1 (12.6 - 21.8)	16	30.9 (26.3 - 41.2)	6	7.8 (6.1 - 11.9)	6	15.7 (10.7 - 19.9)
EHS +/- MPVI	12	13.4 (6.3 - 21.8)	12	19.2 (14.0 - 32.3)	3	5.4 (5.1 - 10.5)	3	12.1 (10.7 - 12.1)
		P=0.75		P=0.25		P=0.19		P=0.47
MPVI								
Yes	4	19.7 (11.9 - 19.7)	4	ND	1	5.1 (ND)	1	12.1 (ND)
No	24	15.4 (12.0 - 21.8)	24	26.3 (17.8 - 32.3)	8	7.8 (5.4 - 11.9)	8	15.7 (10.7 - 19.9)
		P=0.28		P=0.21		P=0.09		P=0.51

Table1. *Median PFS1+2 and OS across Sorafenib-TKI and IO –Sorafenib sequences according to baseline characteristics.*

CONCLUSIONS

- In our series, Sor-TKI performed as the most effective sequence, showing mOS consistent with available data [2,3,7].
- Starting with IO didn't seem to achieve a comparable efficacy, probably due to a weaker disease control of IO in 1L (although the small sample size of our analysis must be considered).
- In order to magnify the clinical benefit of a sequential strategy, additional research on 1L combinations (antiVEGF+IO or TKI+IO) is strongly warranted.

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