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Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution

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Background and Aims

- Success of antiviral therapy against Hepatitis C with direct acting antivirals (DAA)
  - SVR12 in 95 - 97 % in compensated cirrhosis and 85 – 95 % in more advanced liver disease
  - Better results and less side effects than interferon regimens
- Many different subgroups of patients treated including HCC patients
- High expectations in DAA
  - Cirrhosis & need for transplant ↓
  - Cancer ↓
- BUT limited data on long-term outcome, especially in specific subgroups

Patients and Methods

- Observational study in four Spanish referral hospitals (Oct 14 – Dec 15 -> Feb 16)
- Patients with treated HCC before starting antiviral therapy with DAA
- Inclusion criteria:
  - HCC diagnosed by pathology or non-invasive according to current guidelines
  - HCC treated by resection, ablation or chemoembolization before
  - HCC in complete response and absence of non-characteristic nodules
  - Tumor status assessment after starting antiviral therapy
- Exclusion criteria:
  - prior history of liver transplantation
  - patients receiving interferon (IFN) as part of the antiviral regimen.

Observation

- History of HCC before DAA
- HCC treated and under complete response
- DAA treatment for HCV
- Confirmed radiologic assessment after DAA treatment
- Median follow-up 5.7 months [0.4 – 14.6] after DAA initiation

Results

	Total Cohort (n=58)
Age, median [range] (years)	66.3 [45-83]
Gender , n (%)	Male: 40 (69)
Cirrhosis, n (%)	55 (94.8)
Child-Pugh, n (%)	A: 50 (91) / B: 3 (5.4) / C: 2 (3.6)
BCLC	0: 16 (27.6) / A: 42 (72.4)
ASAT, median (IU/ml)	82.5
ALAT, median (IU/ml)	85
AP, median (IU/ml)	104.5
GGT, median (IU/ml)	74
PT, median (%)	76.5
Bilirubin, median (mg/dl)	1.00
Albumin, median (g/l)	40
Creatinine, median (mg/dl)	0.75
Haemoglobin, median (mg/dl)	14.1
Platelets, median ($x10^9$/L)	101
AFP, median (mg/dl)	11.45

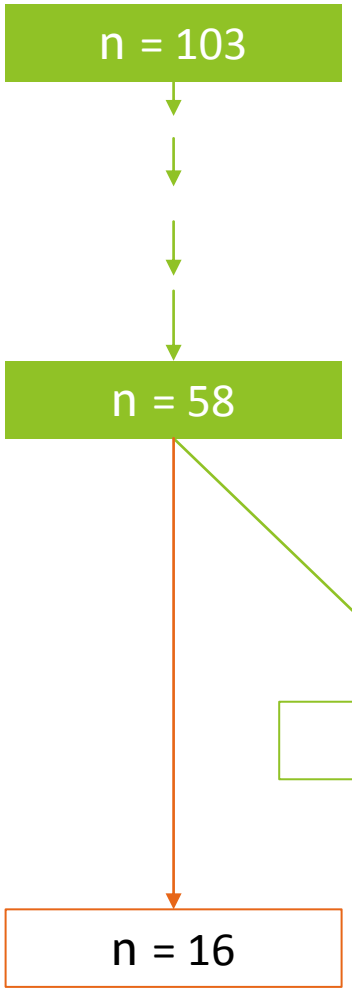
Results

HCV genotype, n (%)	Total Cohort (n=58)
- GT1a	8 (13.8)
- GT1b	45 (77.6)
- GT3	2 (3.4)
- GT4	3 (5.2)

Results

	Total cohort (n = 58)
Naïve / Treatment experienced	29 / 29
HCV RNA, log(10) (IU/ml)	6.08
DAA combination	
- SOF/LDF	21
- 3D	15
- SOF/SMF	15
- SOF/ DCV	6
- SMV/ DMV	1
Use of RBV, n	48
Treatment duration	12 w: 44/ 24 w: 14
HCC treatment before DAA, n (%)	
- Resection	20
- Ablation	32
- TACE	6

Observation



- History of HCC before DAA
- HCC treated and under complete response
- DAA treatment for HCV

- Confirmed radiologic assessment after DAA treatment

- Median follow-up 5.7 months [0.4 – 14.6] after DAA initiation

- HCC complete response

HCC recurrence in 27,6 %

Median time from DAA start to recurrence was 3.5 months [1.1 – 8]

Results

- The pattern of recurrence was heterogeneous: 13 patients developed intrahepatic growth that in 10 cases had a nodular profile (one nodule in 5 of them, up to 3 nodules less or equal to 3 cm in 4 cases, and multifocal in one patient), while 3 patients developed infiltrative ill-defined HCC and/or extrahepatic lesions.
- Median time between HCC treatment and start of DAA:11.2 months [P25-75: 3.6 – 23.2]
  Subgroup with **short time span between HCC treatment and DAA therapy**:
  7 of 17 patients (41.17%) developed radiologic tumor progression
- Subgroup analysis of patients **treated by surgical resection** (→pathology available)
  50% (2/4) of high risk profile vs. 31% (5/16) of low-risk profile presented recurrence.
- Overall survival: 94,8%
  3 Patients died (5,2%): 1 with recurrence, 2 presented complete response but developed cirrhosis complications during the DAA treatment.

Discussion

- We describe a surprisingly high recurrence rate as compared to the already known incidence in patients with successfully treated HCC.
- In Comparison with STORM trial (27,5% of patients HCV only) probability of recurrence vs.
  - In ablation cohort for small HCC 2.45% (4/163) at 4 months and 27.6% (45/163) at 12 months,

27.6% vs.

  - In the surgical study at 4 months is 13.5% [high risk] and 3.8% [low risk]
- Subgroup of ≤ 4 months between HCC treatment complete response verification and DAA treatment initiation:
  - 41.2 % vs. 21.5%/17.6%
- Same difference also when stratifying for other parameters (Child-Pugh, risk profile in pathology or specific DAA agent received) but to few cases

→ Close time association between DAA HCV eradication and recurrence recognition

- Direct enhancing effect of DAA on tumor cell growth cannot be totally discarded it is highly unlikely.
- BUT disruption of immune surveillance system by DAA?
- By modification of the inflammatory process that is in place during viral infection and its modification by effective therapy?
- Immunsuppression at the end of inflammatory processes (e.g. In some respiratory viruses)
- Serti et al. DAA normalizes IFN and innate immunity in chronic Hep C
- Meininger et al. HCV clearance with Sofosbuvir and Ribavirin is accompanied with hepatic downregulation of type II and II interferons, their receptors and interferon stimulated genes AND
  reestablishment of IFN homeostasis is associated with SVR

Conclusion

- Comparison to Interferon-based therapy
  - Different kinetics of viral suppression and associated inflammation
  - Immunostimulation against infective and malignant diseases by IFN
- Raise awareness for more ambitious pharmacovigilance and follow-up after primary end-point evaluation
- Disruption of immune surveillance system is associated with the unleash of of dormant or preclinical clones of malignant cells?
- Now that the available agents offer a major hope for current and future patients, we may face a drawback that may change these predictions in specific groups of patients

→ Priming a large-scale assessment that exceeds the individual investigators capacity

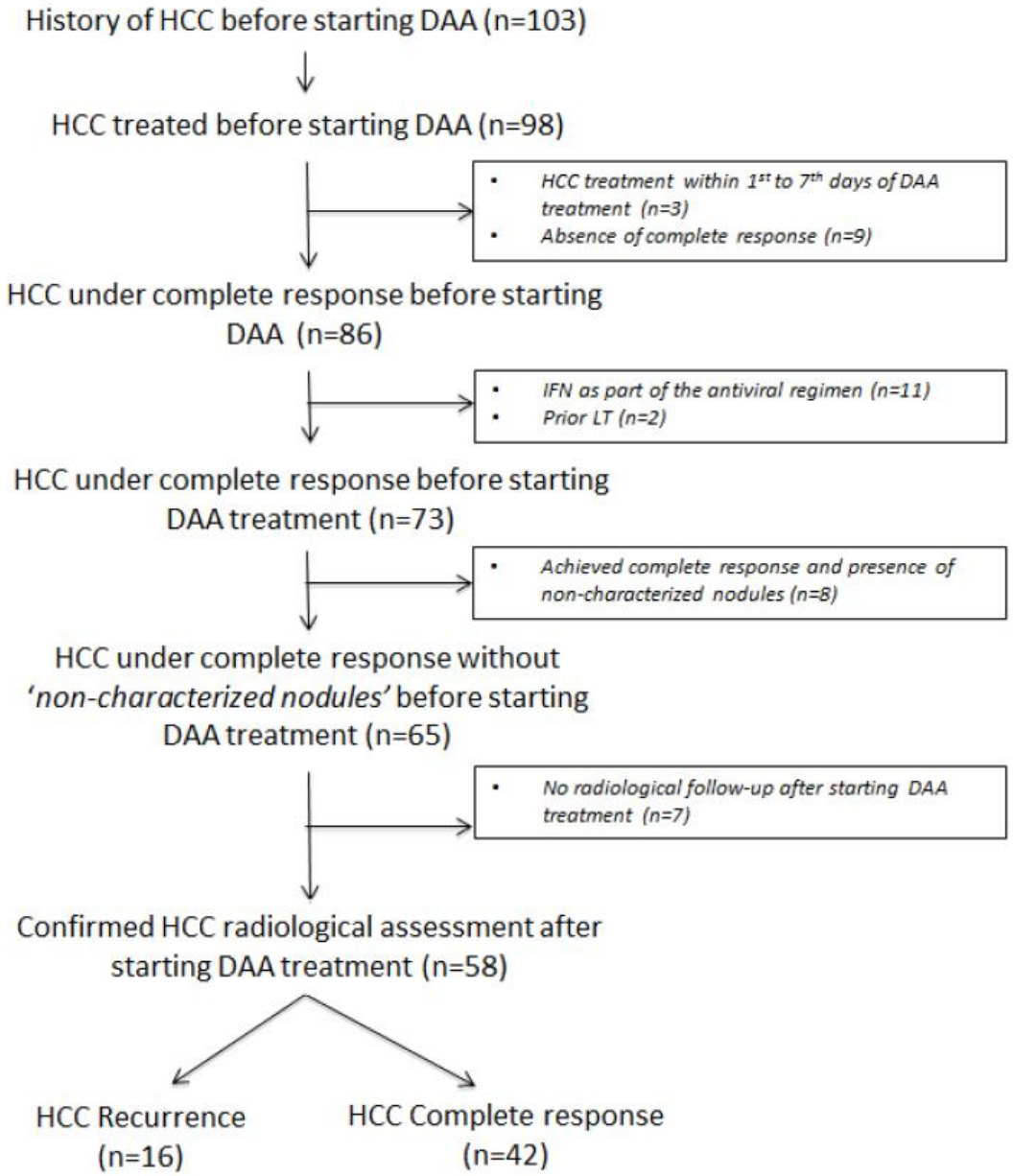

History of HCC before starting DAA (n=103)
HCC treated before starting DAA (n=98)
HCC treatment within 1st to 7th days of DAA treatment (n=3)
Absence of complete response (n=9)
HCC under complete response before starting DAA (n=86)
IFN as part of the antiviral regimen (n=11)
Prior LT (n=2)
HCC under complete response before starting DAA treatment (n=73)
Achieved complete response and presence of non-characterized nodules (n=8)
HCC under complete response without 'non-characterized nodules' before starting DAA treatment (n=65)
No radiological follow-up after starting DAA treatment (n=7)
Confirmed HCC radiological assessment after starting DAA treatment (n=58)
HCC Recurrence (n=16)
HCC Complete response (n=42)

Table 2: Liver function and tumor-related variables of patients with HCC recurrence at the three relevant time points of the study:

	At time of HCC treatment			At time of starting DAA		At time of HCC recurrence afterDAA	
Patient	**PS**	**Child-Pugh**	**BCLC**	**PS**	**Child-Pugh**	**PS**	**Child-Pugh**
1	0	5	A (one nodule)	0	5	0	5
2	0	6	A (one nodule)	0	8	2	8
3	0	6	0	0	5	0	5
4	0	6	A (one nodule)	0	5	0	6
6	0	NA*	A (one nodule)	0	NA*	0	NA*
7	0	5	A (one nodule)	0	5	0	5
8	0	6	A (multiple)	0	6	0	6
9	0	5	A (one nodule)	0	5	0	5
10	0	6	A (one nodule)	0	6	0	5
11	0	5	A (one nodule)	0	5	0	5
12	0	5	A (multiple)	0	5	0	5
13	0	5	A (one nodule)	0	5	0	5
14	0	5	0	0	7	3	7
15	0	7	A (one nodule)	0	10	0	12
16	0	6	0	0	6	0	6

Abbreviations: HCC: hepatocellular carcinoma; DAA: direct-acting antivirals; PS: performance status; BCLC: Barcelona Clinic Liver Cancer;

*Non-cirrhotic patient.

Table 3: Baseline characteristics and outcome of the 16 patients with hepatocellular recurrence.

Patient	Treatment of HCC before DAA	Risk profile at pathology*	At time of starting DAA		At the time of HCC recurrence		HCC Treatment	Status at the end of follow-up
			BCLC	AFP (ng/dl)	Pattern of progression	AFP (ng/dl)		
1	Resection	Low risk	A	91	NIH (one nodule)	912	Resection	Alive
2	**Resection**	**Low risk**	**A**	**18**	**NIH (multinodular)**	42	**BSC**	**Dead**
3	Resection	Low risk	0	2.3	NIH (one nodule)	127.1	Resection	Alive
4	Resection	Low risk	A	12	NIH (≤3 nodules ≤3 cm)	5	Ablation	Alive
5	Resection	Low risk	A	4.2	NIH (≤3 nodules ≤3 cm)	2.1	OLT	Alive
6	Resection	High risk	A	1	NIH (one nodule)	112	Ablation	Alive
7	Resection	High risk	A	8	NIH (one nodule)	6	OLT	Alive
8	**Ablation**	NA	**A**	**38**	**NIH (infiltrative) + NEH****	21184	**Sorafenib**	Alive
9	Ablation		A	66.2	IHG	7.9	Ablation	Alive
10	**Ablation**		**A**	**3**	**NIH (infiltrative) *****	NA	**BSC**	Alive
11	Ablation		A	21.2	IHG	10.2	Ablation	Alive
12	Ablation		A	6.7	NIH (one nodule)	3.8	OLT	Alive
13	Ablation		A	14	IHG	5	Ablation	Alive
14	**Ablation**		**0**	**369**	**NIH (infiltrative) + NEH**	NA	**BSC**	Alive
15	Ablation		A	5	NIH (≤3 nodules ≤3 cm)	8	OLT	Alive
16	Ablation		0	26	NIH (≤3 nodules ≤3 cm) ****	26	Ablation	Alive

BCLC: Barcelona Clinic Liver Cancer; CHC: carcinoma hepatocellular; DAA: direct-acting antivirals; TACE: transarterial chemoembolization; IHG: intrahepatic growth; EHG: extra-hepatic growth; NIH: new intrahepatic lesion; NEH: new extra-hepatic lesion and/or vascular invasion; OLT: orthotropic liver transplantation; BSC: best supportive care; AFP: alpha-fetoprotein.

* Low risk, patients without microvascular invasion and satellites; High risk, patients with microvascular invasion or satellites in pathology.

** Portal vein thrombosis

*** The patient presented an infiltrative HCC and developed early tumor progression with biliary tract invasion.

**** Early tumor progression, the patient received TACE and the last radiologic evaluation describes a 10 cm HCC with macrovascular invasion.

Table 1: Baseline characteristics of the whole cohort

	Total cohort (n =58)
Age, median [range] (years)	66.3 [45- 83]
Gender, (M/F), n (%)	40 (69) /18 (31)
Non cirrhosis/ cirrhosis, n (%)	3 (5.2)/ 55 (94.8)
Child-Pugh, A/B/C, n (%)	50 (91)/ 3 (5.4)/ 2 (3.6)
BCLC stage, 0/A, n (%)	16 (27.6)/ 42 (72.4)
ASAT, median [range] (IU/L)	82.5 [23-433]
ALAT, median [range] (IU/L)	85 [28-487]
AP, median [range] (IU/L)	104.5 [39-357]
GGT, median [range] (IU/L)	74 [21-1181]
PT, median [range] (%)	76.5 [12.60-100]
Bilirubin, median [range] (mg/dl)	1.00 [0.30-6.00]
Albumin, median [range] (g/L)	40 [20-50]
Creatinine, median [range] (mg/dl)	0.75 [0.40-2.37]
Haemoglobin, median [range] (g/dl)	14.1 [8.00-18.50]
Platelets, median [range] (x 10^9 /L)	101 [33-229]
AFP, median [range] (ng/ml)*	11.45 [1- 369]
HCV genotype, n (%)	
- GT1a	8 (13.8)
- GT1b	45 (77.6)
- GT3	2 (3.4)
- GT4	3 (5.2)
Naïve/ Treatment Experienced	29 (50)/ 29 (50)
Previous triple therapy (PR+DAA)**	6 (20.6)
HCV-RNA (Log_{10}) (UI/mL)	6.08 (3.11- 6.92)
DAA combination, n (%)	
- SOF/LDV	21 (36.2)
- 3D	15 (25.9)
- SOF/SMV	15 (25.9)
- SOF/DCV	6 (10.3)
- SMV/DCV	1 (1.7)
Use of RBV, n (%)	48 (82.8)
Treatment duration 12w/ 24w, n (%)	44 (75.9)/ 14 (24.1)
HCC treatment before DAA, n (%)	
Resection	20 (34.5)
Ablation	32 (55.2)
TACE	6 (10.3)