World Cancer Research Journal WCRJ 2016; 3 (3): e748

HEPATOCELLULAR CARCINOMA IN HCV CIRRHOSIS AFTER VIRAL CLEARANCE WITH DIRECT ACTING ANTIVIRAL THERAPY: PRELIMINARY EVIDENCE AND POSSIBLE MEANINGS

L. RINALDI[1], R. DI FRANCIA[2], N. COPPOLA[3], B. GUERRERA[1], M. IMPARATO[4], C. MONARI[3], R. NEVOLA[1], V. ROSATO[1], L. FONTANELLA[4], G. FRANCI[5], G. PORTA[1], V. MESSINA[6], A. ASCIONE[4], L.E. ADINOLFI[1]

[1]Department of Medical, Surgical, Neurological, Metabolic and Geriatric Sciences, Second University of Naples, Naples, Italy
[2]Department of Hematology, National Cancer Institute, G. Pascale, Naples, Italy
[3]Department of Mental and Physical Health and Preventive Medicine, Second University of Naples, Naples, Italy
[4]Department of Internal Medicine, Centre for Liver Disease, Buon Consiglio Fatebenefratelli Hospital, Naples, Italy
[5]Department of Experimental Medicine, Second University of Naples, Naples, Italy
[6]Infectious Disease Unit, AORN S. Anna e S. Sebastiano, Caserta, Italy

Abbreviations: *Hepatocellular carcinoma (HCC), non-alcoholic fatty-liver-disease (NASH), sustained virological response (SVR), direct-acting antivirals (DAA), Italian Medicines Agency committee (AIFA), Child-Turcotte-Pugh (CTP), American Association for the Study of Liver Disease (AASLD), computed tomography (CT), magnetic resonance imaging (MRI), body mass index (BMI), Barcelona Clinic Liver Cancer (BCLC), American Food and Drug Administration (FDA), European Medicines Agency (EMA).*

Abstract – *Background and AIM* *Hepatocellular carcinoma (HCC) is a frequent complication of HCV liver cirrhosis. The reduction of risk after the clearance of HCV-RNA is debated. The aim of our study was to detect the appearance of HCC during the follow-up after antiviral treatment with direct acting antiviral therapy.*

Patients and Methods: *In four specialist Centers, 280 HCV patients were analyzed. The choice of the regimen was based on genotype and stage of liver disease. Abdomen ultrasonography was performed prior, at the end of therapy, and after six months. Biochemistry, BMI, presence of comorbidity, and any complications of related to cirrhosis were also evaluated.*

Results: *Nine HCC were found by ultrasonography (5 cases at the end of therapy, 4 cases 3 months after the end of follow-up); in all cases, HCC was confirmed by a second level imaging examination (computed tomography or magnetic resonance). Characteristics of patients were: male (66.9%; range 56-77), BMI (median 25.4; range 21-40). Prevalence of diabetes was 55.2%. Genotypes were: 1b (6 patients), 1a (2 patients), 2a/2c (1 patient). The therapies were: sofosbuvir plus simeprevir (1 patient), sofosbuvir plus simeprevir plus ribavirin (2 patients), sofosbuvir plus daclatasvir plus ribavirin (2 patients), sofosbuvir plus ribavirin (2 patients), Viekirax + Exviera plus ribavirin (2 patient). One patient only experienced a viral relapse at week 12 after the end of therapy. The incidence of HCC was 3.2%.*

Conclusions: *In patients with liver cirrhosis, even if HCV replication stops, a close follow-up with ultrasonography is mandatory. Since the cumulative incidence is high, a greater sample size is necessary to clarify if the interferon-free antiviral therapy had an influence on the onset of HCC.*

KEYWORDS: *Hepatocellular carcinoma, HCV, Direct acting antiviral, Sustained virological response, Liver cirrhosis, Ultrasound follow-up.*

Corresponding Author: Luca Rinaldi, MD; lucarinaldi@hotmail.it

INTRODUCTION

HCC is one of the leading causes of death from cancer in the world[1]. Its appearance is mainly linked to the presence of liver cirrhosis[2]. The hepatitis viruses, HBV and HCV are major etiological factors of chronic hepatitis and fibrosis[3]. Vaccination coverage for HBV has significantly reduced the amount of cases of advanced liver disease and HBV-related HCC[4].

Recently the role of non-alcoholic fatty-liver-disease (NASH) was highlighted as a risk factor for HCC[5].

The HCV infection is, however, still a current risk factor for HCC. The HCV virus, unlike the HBV virus, does not integrate into the genome and its oncogenic power seems to be related primarily to the effect of chronic inflammation with the progressive development of fibrosis and cirrhosis[6]. The average time between infection and the development of cirrhosis is about 20-30 years; a variable proportion of patients with HCV cirrhosis develop HCC with a very wide range of annual incidence of between 1-8%[7].

Some factors identified which are associated with increased risk of HCC include the duration of fibrosis[8], age, sex, platelet counts, levels of HCV-RNA[9]. However, even some HCV viral components may have direct oncogenic effects; in fact, viral proteins can induce effects of deregulation of the host cells, the DNA mutations of infected cells, and cause immune-mediated oxidative stress[10].

BACKGROUND

Therapies based on interferon and ribavirin accounted, until a few years ago, the only drug scheme available for viral clearance; reaching, in some cases, a sustained virological response (SVR), allowing the prevention of decompensation and the other major failure events related to the advanced disease[11]. Also, the long-term studies have found a reduction in the incidence of HCC over time, but without complete elimination of the risk[12]. Recently, new antiviral therapies with interferon-free medications have been introduced, such as the direct-acting antivirals (DAA) treatments, which have shown a high effectiveness with SVR rates above 90%[13-14]. Such therapies stop the necro-inflammatory activity, preventing the progression of fibrosis to cirrhosis and possibly reducing the risk of HCC[15].

Currently, in Italy, the prescription status of DAA is reserved for advanced forms of liver disease such as severe fibrosis (F3 Metavir) and cirrhosis (F4 Metavir). The very high cost of medications limits the therapy to patients who are in high-risk categories; this implies that a large part of the population that undertakes therapy with DAA is already at the stage of cirrhosis. The high rate of viral clearance achieved with DAA turns off the necro-inflammatory activity and through the stimulus chronic irritation; however, the inveterate cirrhotic architecture is a condition difficult to reverse and is potentially oncogenic[16]. These components comprise a possible residual risk of HCC, and therefore cannot be established, at present, which is the real influence of the DAA. The purpose of this study was to analyze the possible HCC appearance in cirrhotic patients after HCV viral clearance by DAA drugs.

PATIENTS AND METHODS

Two hundred and eighty HCV patients were observed in four Italian specialistic Centers. The monitoring period was between January 2015 and February 2016.

HCV-RNA was assessed by PCR real-time before the treatment and at the end of it. The technical platform for HCV-RNA detection is based on dual labelled fluorescent probe. The test is performed in accordance with the CE-IVD policy following the manufacturers, using real-time PCR with a limit of detection of 15 IU/mL.

The choice of the regimen with DAA (12/24 weeks) was based on genotype and stage of liver disease, according to the national registry of the Italian Medicines Agency committee (AIFA). Approved criteria included: patients with Child-Turcotte-Pugh (CTP) class A or B liver cirrhosis, without history of previous HCC or with history of HCC with complete radiologic response (after surgical resection or locoregional ablation); and patients with a METAVIR F3 fibrosis score, assessed by liver histology or transient elastography by Fibroscan® (Echosens, Paris, France), result > 12 kPa.

The SVR is considered the absence of HCV-RNA at 12 weeks after the end of therapy.

The diagnosis of HCC was based on American Association for the Study of Liver Disease (AASLD)-guidelines[17]. For patients with no previous history of HCC, an ultrasound screening was carried out. Abdomen ultrasonography was performed prior to starting therapy. The maximum amount of time that passed between the liver ultrasound and the beginning of treatment was ten days. For patients with prior history of HCC treated, a dynamic and multiphase contrast-enhanced computed tomography (CT) or

hepatospecific contrast agent Magnetic Resonance Imaging (MRI) was conducted prior to initiating therapy.

Patients with a dubious focal lesion, which were detected prior to starting the therapy were excluded. In addition, patients with co-infection with HBV and HIV and HCV positive patients after liver transplantation were also excluded. Antiviral regimens containing interferon were not considered. At the end of therapy and after six months, an ultrasound was conducted again; in the case of an appearance of a lesion, a CT scan or MRI examination was conducted. Biochemistry, body mass index (BMI), liver stiffness, presence of comorbidity, and any complications related to cirrhosis were also evaluated.

Statistical Analysis

Quantitative variables were expressed as median and range or percentile 25-75 (P25-75); the categorical variables as count number and proportions. All calculations were done with SPSS package version 23 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the population and antiviral treatment

A total of 280 patients were evaluated; demographic baseline characteristics at the start of therapy with DAA are summarized in the Table I. In particular, the majority of patients were males (53%), mean aged 68 (range 35-84 years), with prevalent HCV genotype 1 infection (76%), and CTP A (86.8%). As for severity of the liver disease, 28 patients (13.2%) were classified as CTP class B at the start of DAA treatment. Two patients died of cardiac causes during treatment and two patients discontinued treatment before the deadline. Two hundred and seventy-two (97.1%) patients obtained viral clearance and SVR at follow-up, after the completion of a course of therapy with DAA. Only four patients (1.4%) had a recurrence of HCV-RNA, which was detected at three months follow-up. Treatment regimens are illustrated in Table I. Fifteen patients had a previous history of HCC, with a complete radiological response at the start of DAA therapy, according to AASLD criteria. To limit the confounding factors, cases of non-characterized hepatic lesions were not considered. All patients didn't show active lesion of HCC at the start of antiviral therapy.

TABLE 1. Demographic baseline characteristics at the start of therapy with DAA.

Males n, %	148 (53%)
Age, yrs. median, range	68 (35-84)
HCV genotype 1 n, %	213 (76%)
Child- T-Pugh A n, %	243 (86.8%)
B n, %	37 (13.2%)
History of previous HCC, n. %	15 (5.3%)
Antiviral therapy n, %	280 (100%)
SOF/SIM/RIBA	78 (27.9%)
SOF/RIBA	32 (11.5%)
3D/RIBA	22 (7.7%)
SOF/DAC/RIBA	14 (4.8%)
SOF/SIM	48 (16.9%)
3D	55 (19.7%)
HARVONI	30 (11%)
HARVONI/RIBA	1 (0.5%)

Abbreviations. DAA: direct-acting antivirals; SOF: sofosbuvir; SIM: simeprevir; RIBA: ribavirin; 3D: ombitasvir/paritaprevir/ritonavir – dasabuvir; DAC: daclatasvir; Harvoni: Ledipasvir-sofosbuvir

Follow-up and hepatocellular carcinoma

The median follow-up was 12 weeks (range 3-24 weeks); during which nine HCC were found. The incidence of HCC in this cohort was 3.2% (95% CI: 1.2- 5.2). The HCC was detected by ultrasonography with a median from the end of treatment of 1 month (range 0-3 months).

In particular, 5 cases were found at the end of therapy, and 4 cases 3 months after the end of antiviral therapy; in all cases, HCC was confirmed by a second level imaging examination (CT or MRI). HCC with single nodule were 7 (77.7%). Eight cases out of 9 (88.9%) developed HCC for the first time, while one (11.1%) of the 9 patients had an early recurrence of HCC.

The distance between the treatment of HCC and the beginning of therapy with DAA was 49 weeks. Characteristics of these patients were: male 66.9%, age (median 69; range 56-77), BMI (median 25.4; range 21-40). Prevalence of diabetes was 55.2%. Genotypes were: 1b (6 patients), 1a (2 patients), 2a/2c (1 patient).

The antiviral therapies were: sofosbuvir plus simeprevir (1 patient), sofosbuvir plus simeprevir plus ribavirin (2 patients), sofosbuvir plus daclatasvir plus ribavirin (2 patients), sofosbuvir plus ribavirin (2 patients), Viekirax + Exviera plus ribavirin (2 patients). CTP A was 77.7%(Table 2). The Barcelona Clinic Liver Cancer (BCLC) stage system was used for staging the HCC and it was illustrated in Table 3.

TABLE 2. Sequences of primers for real-time PCR.

Patients n.	Age (years)	Sex	BMI	Diabetes	Geno-type	Child-T-Pugh	Treatment with DAA	Weeks of therapy
1	69	M	27.6	YES	1b	A6	SOF/SIM/RIBA	12
2	68	F	21	YES	2ac	A6	SOF/RIBA	16
3	77	M	24.9	NO	1b	A6	3D/RIBA	12
4	56	M	26	NO	1a	B8	SOF/DAC/RIBA	24
5	69	M	25.4	YES	1b	A5	SOF/SIM/RIBA	24
6	74	F	22.2	NO	1a	A5	SOF/DAC/RIBA	24
7	69	F	40	YES	1b	A6	SOF/SIM	12
8	68	M	25	YES	1b	A5	SOF/RIBA	12
9	62	M	27	NO	1b	A6	3D/RIBA	24

Abbreviations: BMI: body mass index; DAA: direct-acting antivirals; SOF: sofosbuvir; SIM: simeprevir; RIBA: ribavirin; 3D: ombitasvir/paritaprevir/ritonavir – dasabuvir; DAC: daclatasvir

Only one patient with the appearance of HCC experienced a viral relapse at week 12 after the end of therapy. None of the patients have signs of extrahepatic manifestations of HCC.

DISCUSSION

The SVR to antiviral therapy with DAA is more than 90% and we expect a lack of progression of the chronic liver disease and a significant reduction in complications of cirrhosis.

The interferon-based therapies performed from over twenty years have allowed a long-term evaluation of the effects on HCV patients. There is evidence that the therapy turned off necro-inflammatory and reduced decompensation as ascites, hepatic encephalopathy, and variceal bleeding[18-20]. Furthermore, the incidence of HCC appeared reduced, but there is still the risk, as demonstrated in several papers[16]. The recent introduction of the DAA did not allow a long-term evaluation of the impact on the incidence of HCC[21].

Our study was conducted on a population of 280 patients treated in four centers of southern Italy. The characteristics of our cohort are similar to the general population with chronic HCV hepatitis: prevalence of genotype 1, fibrosis 4 Metavir score, prevalence of Child A, high viral load[22]. The follow-up of patients in the first few months

TABLE 3. Characteristic of patients with appearance of HCC during follow-up.

Patients n.	HCC before DAA	End of therapy		6 months of follow-up		Portal invasion	HCC treatment
		HCC	BCLC	HCC	BCLC		
1	Yes *	Yes	A one nodules	–		No	RF-ablation
2		Yes	C one nodule	–		Yes	Sorafenib
3		Yes	B two nodules	–		No	TACE
4		Yes	C one nodule	–		Yes	Sorafenib
5		No		Yes	A one nodule	No	RF-ablation
6		No		Yes	A one nodule	No	RF-ablation
7		No		Yes	A one nodule	No	RF-ablation
8		No		Yes	A one nodule	No	–
9		No		Yes	A one nodule	No	RF-ablation

*treated by percutaneous radio-frequency ablation
Abbreviations: DAA: direct-acting antivirals; BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemo embolization therapy, RF: radio-frequency

of therapy confirmed a high rate of SVR (97.1%). However, the most surprising event was the finding of nine HCC in the early weeks following therapy with an incidence of 3.2%; in particular, half the HCC cases occurred at the end of the anti-viral treatment. Also one of the cases had a recurrence of a previously treated HCC.

This result does not differ from that detected in the inveterate cirrhotic population[3,6-7]. Since this result was obtained by a small cohort of patients, further evaluation is required. The absence of HCC at ultrasound check up performed before treatment, does not totally exclude the presence of a pre-existing focal lesion. However, the fast effects of the DAA on viral clearance and inhibition of inflammatory activity would theoretically provide a protective element in cell proliferation[15].

Characteristics of patients who developed HCC do not differ from the general population, in age, sex, BMI, diabetes prevalence and treatment patterns; genotype 1 is prevalent as in the rest of the cohort. HCC appeared as a single lesion in eight patients, while in one patient we detected two lesions during the follow-up; furthermore, in two patients it was detected portal invasion at the end of treatment.

This rapid occurrence of neoplastic proliferation considering the short time of follow-up of just three months is unusual. In a recent study, Bruix et al[23] found 27% of HCC recurrence in patients with previous treatment for HCC in the follow-up at a short distance after the end of therapy with DAA. In a recent Italian report, by Brillanti et al[24], 344 patients were monitored for 24 weeks, resulted in an incidence of 7.6% of HCC. In uni- and multivariate analysis, HCC was independently associated with the CTP class and presence of prior HCC. These studies confirm that both the viral clearance and the shutdown of the necro-inflammatory activity are not sufficient element to reduce the risk of HCC; furthermore, the occurrence of cases in the first few weeks from the ending of antiviral treatment suggests the presence of unrecognized mechanisms of factors inducing HCC.

Finally, these new drugs developed for HCV-patients are a result of the continued research in this field. Recently, the American Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recognized the clinical value of genetic variants in metabolic pathways and have developed guidelines for industry concerning pharmacogenetics data submission with new drugs[25]. Current knowledge of pharmacogenomics has increased individualized therapy adjusted in accordance with the patient's genetic profile. Furthermore, substantial knowledge of pharmacogenomics is a prerequisite for its application to clinical practice, to prevent the drug-drug interaction based on individual metabolic-genetic profiles[26-28].

This approach could allow the use of new natural remedial in addition to conventional therapies either to prevent or minimize toxicity[29]. Over the next few years, the emergence of drug-drug interactions in the new therapies as results of genomic alteration (i.e. anti-HCV concomitant to cancer), will drive diagnostics companies to develop new tests which will be able to produce results that are indicative for tailoring a patient's treatment[30].

In the 3rd millennium, the promise that the pharmaceutical and biotechnological companies should keep is that they will join together, in order to develop a specific test suitable for genotyping and phenotyping the individual metabolic profile of HCV-patients[31].

CONCLUSIONS

At this stage, it is impossible to say if DAA had an influence on the appearance of HCC. Further studies with greater sample size are necessary to clarify this issue.

Acknowledgement:
Stefania Milione MD, Second University of Naples, for the cooperation. This is a spontaneous study and has not been supported by specific funding.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. Bruix J, Reig M, Sherman M. Evidence-based, diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016; 150: 835-853.
2. Wang Y, Li J, Chen J, Liu L, Peng Z, Ding J, Ding K. From cirrhosis to hepatocellular carcinoma in HCV-infected patients: genes involved in tumor progression. Eur Rev Med Pharmacol Sci 2012; 16: 995-1000.
3. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006; 45: 529-538.
4. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, Wu SF, Lee CM, Yang SS, Chu HC, Wang TE, Chen BW, Chuang WL, Soon MS, Lin CY, Chiou ST, Kuo HS, Chen DS; Taiwan Hepatoma Study Group. Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. Gastroenterology 2016; 151: 472-480.e1.

5. Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, Bellentani S. HCC-NAFLD Italian Study Group. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. Hepatology 2016; 63: 827-838.
6. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment Pharmacol Ther 2010; 32: 344-355.
7. Wirth TC, Manns MP. The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma. Ann Oncol 2016; 27: 1467-1474.
8. Zampino R, Pisaturo MA, Cirillo G, Marrone A, Macera M, Rinaldi L, Stanzione M, Durante-Mangoni E, Gentile I, Sagnelli E, Signoriello G, Miraglia Del Giudice E, Adinolfi LE, Coppola N. Hepatocellular carcinoma in chronic HBV-HCV co-infection is correlated to fibrosis and disease duration. Ann Hepatol 2015; 14: 75-82.
9. Pinzone MR, Zanghì AM, Rapisarda L, D'Agata V, Benanti F, Spartà D, Nunnari G, Cacopardo B. Cirrhotic patients are still at risk of developing hepatocellular carcinoma despite Interferon-induced sustained virological response. Eur Rev Med Pharmacol Sci 2014; 18 (2 Suppl): 11-15.
10. Lemon SM, McGivern DR. Is hepatitis C virus carcinogenic? Gastroenterology 2012; 142: 1274-1278.
11. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, Ascione A, Santantonio T, Piccinino F, Andreone P, Mangia A, Gaeta GB, Persico M, Fagiuoli S, Almasio PL; Italian Association of the Study of the Liver Disease (AISF). Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007; 45: 579-587.
12. D'Ambrosio R, Della Corte C, Colombo M. Hepatocellular Carcinoma in patients with a sustained response to anti-hepatitis C therapy. Int J Mol Sci 2015; 16: 19698-19712.
13. Chhatwa J, Wang X, Ayer T, Kabiri M, Chung RT, Hur C, Donohue JM, Roberts MS, Kanwal F. Hepatitis C Disease Burden in the United States in the Era of Oral Direct-Acting Antivirals. Hepatology 2016 Mar 25. doi: 10.1002/hep.28571. [Epub ahead of print].
14. Ioannou GN, Beste LA, Chang MF, Green PK, Lowey E, Tsui JI, Su F, Berry K. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Healthcare System. Gastroenterology. 2016; 151: 457-471.e5.
15. Nunnari G, Montineri A, Portelli V, Savalli F, Fatuzzo F, Cacopardo B. The use of peginterferon in monotherapy or in combination with ribavirin for the treatment of acute hepatitis C. Eur Rev Med Pharmacol Sci 2012; 16: 1013-1016.
16. Berretta S, Fisichella R, Spartà D, Lleshi A, Nasti G. Primary liver cancer: clinical aspects, prognostic factors and predictive response to therapy. WCRJ 2015; 2: e561.
17. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.
18. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N; SOLAR-1 Investigators. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology 2015; 149: 649-659.
19. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, Reddy KR, Lawitz E, Flamm SL, Schiano T, Teperman L, Fontana R, Schiff E, Fried M, Doehle B, An D, McNally J, Osinusi A, Brainard DM, McHutchison JG, Brown RS Jr, Charlton M; ASTRAL-4 Investigators. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med 2015; 373: 2618-2628.
20. Deterding K, Honer Zu Siederdissen C, Port K, Solbach P, Sollik L, Kirschner J, Mix C, Cornberg J, Worzala D, Mix H, Manns MP, Cornberg M, Wedemeyer H. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. Aliment Pharmacol Ther 2015; 42: 889-901.
21. Aprile G, Fanotto V, Garattini S K, Bozza C, De Carlo E, Fontanella C, Bonotto M, Basile D, Cattaneo M, Casagrande M, Ferrari L, Ongaro E, Cardellino GG, Ermacora P, Giovannoni M, Pella N, Fasola G. The concept of maintenance: may we move it to gastric, pancreatic and liver cancers? WCRJ 2016; 3: e713.
22. Serranti D, Buonsenso D, Ceccarelli D, Gargiullo L, Ranno O, Valentini P. Pediatric hepatitis C infection: to treat or not to treat: what's the best for the child? Eur Rev Med Pharmacol Sci 2011; 15: 1057-1067.
23. María R, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016. pii: S0168-8278(16)30113-1
24. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in hcv-related cirrhosis treated with direct acting antivirals. J Hepatol 2016; 65: 727-733.
25. Di Martino S, Rainone A, Troise A, Di Paolo M, Pugliese S, Zappavigna S, Grimaldi A, Valente D. Overview of FDA-approved anti cancer drugs used for targeted therapy. WCRJ 2015; 2: e553.
26. Rainone A, De Lucia D, Morelli CD, Valente D, Catapano O, Caraglia M. Clinically relevant of Cytochrome P450 Family enzymes for drug-drug interaction in anticancertherapy. WCRJ 2015; 2: e524.
27. Di Francia R, Di Paolo M, Valente D, Cacopardo B, Cilenti L. Pharmacogenetic based drug-drug interactions between Highly Active Antiretroviral Therapy (HAART) and antiblastic chemotherapy. WCRJ 2014; 1: e386.
28. Rinaldi L, Milione S, Porta G, Siniscalchi LI, Franci G, Di Francia R. Inhibition of the JNK signaling pathway increases sensitivity of hepatocellular carcinoma cells to cisplatin by down-regulating expression of P-glycoprotein. Eur Rev Med Pharmacol Sci 2016; 20: 2947-2949.
29. Di Francia R, Rinaldi L, Troisi A, Di Benedetto F, Berretta M. Effect of anti-oxidant agents in patients with hepatocellular diseases. Eur Rev Med Pharmacol Sci 2015; 19: 3993-3995.
30. Di Francia R, Fierro C, Di Paolo M, Siesto SR, Cacopardo B, Cilenti L, Atripaldi L. Selected pharmacogenetic panel test for toxicity prevention of drug-drug interactions between Highly Active Antiretroviral Therapy (HAART) and antiblastic chemotherapy. WCRJ 2015; 2: e492.
31. Berretta M, Di Francia R, Tirelli U. Editorial – The new oncologic challenges in the 3RD millennium. WCRJ 2014; 1: e133.