Targ Oncol (2017) 12:61–67
DOI 10.1007/s11523-016-0454-5

ORIGINAL RESEARCH ARTICLE

Impact of Diabetes on Outcomes of Sorafenib Therapy for Hepatocellular Carcinoma

Giovan Giuseppe Di Costanzo[1] · Raffaella Tortora[1] · Filomena Morisco[2] · Luigi Addario[1] · Maria Guarino[2] · Gabriella Cordone[1] · Luigia Falco[1] · Nicola Caporaso[2]

Published online: 9 August 2016

Abstract

Background Patients with diabetes are at increased risk of developing hepatocellular carcinoma (HCC) and have a poorer prognosis as compared to non-diabetics when HCC occurs. Diabetics with non-HCC cancers are at higher risk of toxicity related to systemic therapy, but data on HCC are lacking.

Objective The aim of this study was to evaluate safety and effectiveness of sorafenib in HCC patients according to the presence/absence of diabetes.

Patients and Methods From October 2008 to June 2014, 313 patients with HCC treated with sorafenib were enrolled. The patients were staged according to the BCLC system. Treatment response was evaluated according to the mRECIST criteria. The main evaluated outcomes were the overall survival and the safety in the two groups.

Results Patients were divided in two groups: 80 diabetics (DIAB) and 233 nondiabetics (nDIAB). The median treatment duration was 4 months in DIAB and 3 months in nDIAB. Main adverse events occurred with comparable frequency in both groups, with the exception of rash, that was more frequent among DIAB than in nDIAB: 27.5 % vs 17.6 % ($P = .047$). The median overall survival was 9 months in nDIAB and 10 months in DIAB group ($P = .535$). Median time-to-progression (TTP) was longer the in DIAB than the nDIAB group ($P = .038$).

Conclusions Sorafenib was as safe as effective in DIAB and in nDIAB patients. The longer TTP observed among DIAB than in nDIAB patients might suggest a better anticancer effect of sorafenib in patients with diabetes.

Key Points

Sorafenib in diabetics was safe and the longer TTP observed in diabetics might suggest a better anticancer effect of sorafenib in patients with diabetes.

The better TTP in patients treated with oral therapy as compared to those receiving insulin is interesting and concordant with previous studies on different cancers.

Abbreviations

HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HBV	Hepatitis B virus
EASL	European Association for the study of the liver
BCLC	Barcelona clinic liver cancer
ECOG	Eastern cooperative oncology group
PS	Performance status
AFP	Alpha fetoprotein
US	Ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging
OS	Overall survival
TTP	Time-to-progression
mRECIST	Modified Response Evaluation Criteria in Solid Tumours for hepatocellular carcinoma
CR	Complete response
PR	Partial response

✉ Giovan Giuseppe Di Costanzo
ggdicostanzo@libero.it; dicostanzogg@gmail.com

[1] Department of Transplantation - Liver Unit, Cardarelli Hospital, Via A. Cardarelli 9, 80131 Naples, Italy

[2] Department of Clinical Medicine and Surgery - Gastroenterology Unit, University of Naples "Federico II", Naples, Italy

SD	Stable disease
PD	Progressive disease
DIAB	Diabetics
nDIAB	Nondiabetics
HFS	Hand foot syndrome
TACE	Transarterial chemoembolization

1 Introduction

Hepatocellular carcinoma (HCC) is a leading cause of death for cancer worldwide [1]. In Western countries, HCC occurs in most of cases in patients with cirrhosis, that is, therefore, a preneoplastic state, and is the main cause of death among cirrhotics [2, 3]. Hepatitis C (HCV) and B (HBV) viral infections and alcohol consumption are the main etiological agents. In the last years, nonalcoholic fatty liver disease and steatohepatitis are becoming increasingly recognized causes of cirrhosis and HCC [4]. Metabolic syndrome, mainly obesity and diabetes, is strictly related to the presence of liver steatosis and steatohepatitis [5]. Patients with obesity and type 2 diabetes are at increased risk of developing HCC [6, 7]. A longer duration of diabetes is related to a higher rate of HCC development [8, 9], and diabetes may worsen the outcomes of patients with cirrhosis and HCC [10–13]. Furthermore, impaired carbohydrate metabolism is more frequently observed in cirrhosis than in the general population and about a third of these patients have type 2 diabetes [14].

In spite of more extensive use of surveillance and liver imaging in patients with cirrhosis, a substantial proportion of HCC are diagnosed in intermediate and advanced stage and only 30 % of patients can be treated with potentially curative therapies. Moreover, over time a considerable percentage of early HCC patients progresses to the advanced stage [15]. Therefore, many patients with HCC necessitate systemic treatment, and sorafenib (Nexavar©, Bayer Health Care, Leverkusen, Germany) is the only drug approved worldwide for HCC advanced stage patients who are not candidates to curative treatments [16]. However, systemic therapy in patients with diabetes might be challenging. Patients with diabetes and non-HCC cancers are at higher risk of toxicity related to systemic treatment and often are treated with less aggressive therapies as compared to patients without diabetes [17, 18]. Data regarding HCC patients are lacking and only a small study on patients with metastatic renal cell carcinoma or advanced HCC showed that sorafenib treatment in diabetic patients was safe [19]. Due to the high prevalence and the role of diabetes in HCC these data are necessary and clinically relevant. Therefore, the aim of this field-practice study was to evaluate safety and effectiveness of sorafenib treatment in a large cohort of HCC patients according to the presence or absence of diabetes.

2 Patients and Methods

2.1 Patients

From October 2008 to June 2014, all consecutive patients with unresectable HCC who were treated with sorafenib attending the Liver Unit of Cardarelli Hospital were included in this single centre prospective observational study. The diagnosis of HCC was performed according to the European Association for the Study of the Liver (EASL) criteria [20]. At the time of starting the treatment with sorafenib, the tumor stage was assessed following the Barcelona Clinic Liver Cancer (BCLC) staging system [21]. Patients were treated with sorafenib in case of HCC untreatable with surgery or locoregional therapy, ECOG (Eastern Cooperative Oncology Group) performance status (PS) 0–1, and Child-Pugh score ≤ 7. Starting dose of sorafenib was 800 mg/day, except for patients with bilirubin >2 mg/dL or ascites in whom the dose was reduced to 400 mg/day.

The diagnosis of diabetes was performed when fasting blood glucose was greater than or equal to 126 mg/dl, according to the American Diabetes Association guidelines 2015 [22].

2.2 Assessment Schedule

At baseline, all necessary patient characteristics were evaluated: age, sex, height, weight, clinical information, biochemical parameters, serum alpha-fetoprotein (AFP), upper gastrointestinal endoscopy, abdominal Doppler ultrasound (US), chest computed tomography (CT), and abdominal contrast-enhanced CT or magnetic resonance imaging (MRI). In patients with suspected bone metastasis, a bone scintigraphy was performed. The treatment duration was calculated by summing the days of drug intake, excluding the intervals of temporary discontinuation of sorafenib.

Once a month patients underwent to clinical evaluation, biochemical tests, AFP, abdominal US, pill-count for the evaluation of compliance to treatment, and record of adverse events according to definitions from the National Cancer Institute's Common Toxicity Criteria version 3.0 (http://ctep.info.nih.gov/CTC3/ctc ind term.html), using a pre-planned questionnaire. For a better management of patients, a call centre was available every day to patients for consulting a doctor.

To evaluate radiological response to treatment, CT or MRI scans were performed every 3 months and in any case of suspected progression.

2.3 Outcomes and Assessments

The main evaluated outcomes were the overall survival (OS) and the safety in the two groups.

The OS was measured from the date of starting sorafenib until the date of death or the last visit. The safety was assessed evaluating the occurrence and the grade of sorafenib adverse events.

Secondary outcomes were the 3-month radiological response to sorafenib and the time-to-progression (TTP). The radiological response to sorafenib was evaluated according to the modified Response Evaluation Criteria in Solid Tumours for Hepatocellular Carcinoma (mRECIST) criteria [23]. Response to therapy was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The disease-control rate (DCR) was defined as the percentage of patients who had a best response rating of complete response, partial response, or stable disease.

The TTP was measured from the starting treatment data until the clinical or radiological evidence of disease progression or last follow-up.

2.4 Statistical Analysis

A two-tailed p-value < 0.05 was considered to indicate statistical significance. Categorical data were compared using Fisher's exact test. Continuous variables were shown as median and compared with the non-parametric Mann–Whitney test. Time-to-event data was visualized using Kaplan–Meier curves and compared by the log-rank test. All statistical analyses were performed with software package SPSS for Mac (Rel SPSS 21.0; IBM Corporation, Armonk, NY, USA, 2012).

3 Results

Three hundred thirteen patients with HCC treated with sorafenib were included in the study. Patients were divided in two groups according to the presence of diabetes: 80 diabetics

Table 1 Baseline characteristics of diabetic and nondiabetic patients

Characteristics	DIAB $n = 80$	nDIAB $n = 233$	P
Males	56 (70 %)	175 (75 %)	.379
Median age (range)	68 (41–84)	67 (35–90)	.805
HCV infection	54 (67.5 %)	152 (65.5 %)	.786
HBV infection	9 (11.3 %)	42 (18.0 %)	.157
Alcohol	8 (10.0 %)	15 (6.4 %)	.292
NAFLD	6 (7.5 %)	11 (4.7 %)	.344
Other aetiologies	3 (3.7 %)	13 (5.6 %)	.120
Median BMI, (range)	25 (18–45)	25 (18–35)	.815
Child score 5	45 (56.3 %)	123 (52.8 %)	.145
Child score 6	31 (38.8 %)	80 (34.3 %)	
Child score 7	4 (5 %)	30 (12.9 %)	
Ascites	11 (13.8 %)	35 (15 %)	.856
Bilirubin ≤ 2 mg/dL	76 (95.0 %)	208 (89.3 %)	.179
Albumin ≥ 3.5 g/dL	57 (71.2 %)	174 (74.7 %)	.555
BCLC B	18 (22.5 %)	55 (23.6 %)	.880
BCLC C	62 (77.5 %)	178 (76.4 %)	
Portal thrombosis	41 (51.3 %)	117 (50.2 %)	.897
Extrahepatic metastasis	28 (35.0 %)	76 (32.7 %)	.783
Median AFP ng/mL (range)	313 (2–433,250)	290 (1–741,720)	.690
Previously treated, n	52 (65.0 %)	153 (65.7 %)	1.00
Liver transplantation	1 (1.3 %)	11 (4.7 %)	.772
Surgical resection	3 (3.7 %)	5 (2.1 %)	
Local ablation	10 (12.5 %)	25 (10.7 %)	
TACE	20 (25.0 %)	47 (20.2 %)	
Combined locoregional treatments	18 (22.5 %)	65 (27.9 %)	
No previous treatment	28 (35.0 %)	80 (34.3 %)	
Median treatment duration, months	4 (1–41)	3 (1–56)	.178
Starting sorafenib dose 800 mg/d	71 (88.8 %)	205 (88.0 %)	1.00
Median daily dose	673 mg	622 mg	.496
Median daily dose ≥ 400 mg, n of patients	75 (93.8 %)	203 (87.1 %)	.148
Median survival, months, (95%CI)	10 (7.6-12.4)	9 (7.5-10.5)	.478

Table 2 Side effects to sorafenib treatment in diabetic and nondiabetic patients

Side effects	DIAB Grade 1-2/3-4	nDIAB Grade 1-2/3-4	*P*
Fatigue	48.8 %/3.8 %	45.7 %/3.9 %	.973
Anorexia	47.6 %/1.3 %	38.3 %/2.6 %	.480
HFS	46.3 %/3.8 %	37.1 %/5.2 %	.248
Diarrhea	41.3 %/3.8 %	46.1 %/3.9 %	.818
Arterial hypertension	26.3 %/0 %	25.4 %/0.9 %	.836
Rash	27.5 %/0 %	15 %/2.6 %	**.047**
Weight loss	22.6 %/0 %	19.8 %/0 %	.863
Alopecia	18.9 %/0 %	13.7 %/0 %	.682
Pruritus	17.6 %/0 %	11.2 %/0.9 %	.372
Abdominal pain	17.5 %/0 %	22.2 %/1.7 %	.407
Nausea	15.1 %/2.5 %	14.6 %/0.4 %	.427
Jaundice	10.1 %/6.3 %	17.7 %/5.6 %	.309
Aftosis	10.1 %/0 %	7.3 %/0.9 %	.376
Vomiting	7.6 %/0 %	5.6 %/0.4 %	.756
Bleeding	2.5 %/2.5 %	3.9 %/3.3 %	.685

(DIAB) and 233 nondiabetics (nDIAB). No differences in demographics, liver function, and cancer stage between DIAB and nDIAB groups were observed (Table 1).

All DIAB patients were affected by type 2 diabetes and the treatment was: exogenous insulin in 57.5 %, oral hypoglycemic agents in 28.8 %, acarbose and diet in 13.7 %. After 1–2 cycles of sorafenib, nine (11 %) patients had reduced or stopped blood glucose-lowering drugs due to the decrease in blood glucose level. One patient experienced severe hypoglycaemia.

The median duration of sorafenib treatment was 4 (range 1–41) months in DIAB and 3 (1–56) months in nDIAB.

Adverse events were observed in 96.3 % and in 94 % of DIAB and nDIAB patients, respectively. Main adverse events (fatigue, hand foot syndrome (HFS), diarrhea, and hypertension) occurred with comparable frequency in both groups (Table 2). Rash was the only adverse event more frequent in DIAB as compared to nDIAB: 27.5 % vs 17.6 % ($P = .047$).

Median sorafenib dose was 621 mg/day (range 55–800) in nDIAB and 673 mg/day (range 81–800) in DIAB group ($P = .218$). Sorafenib was temporary and permanently discontinued due to adverse events in 23.2 % and 27.2 % in the nDIAB group, and in 21.3 % and 30.4 % in the DIAB group, respectively.

The median overall survival was 9 months (95 % CI, 7.45-10.55) in nDIAB and 10 months (95 % CI, 7.57-12.43) in DIAB group ($P = .535$) (Fig. 1).

Clinical or radiological progression was observed in 107 (45.9 %) patients of the nDIAB group and in 31 (38.8 %) patients of the DIAB group ($P = .105$). The radiological evaluation of response after 3 months of therapy was available in 199 (63.6 %) of patients (Table 3). The DCR was 71.5 % (103 among 144 patients) and 83.6 % (46 among 55 patients) in the nDIAB and DIAB groups, respectively ($P = .10$). The probability of disease progression at 6-month and 12-month was 44.0 % and 59.4 % in the nDIAB group, 34.7 % and 44.4 %

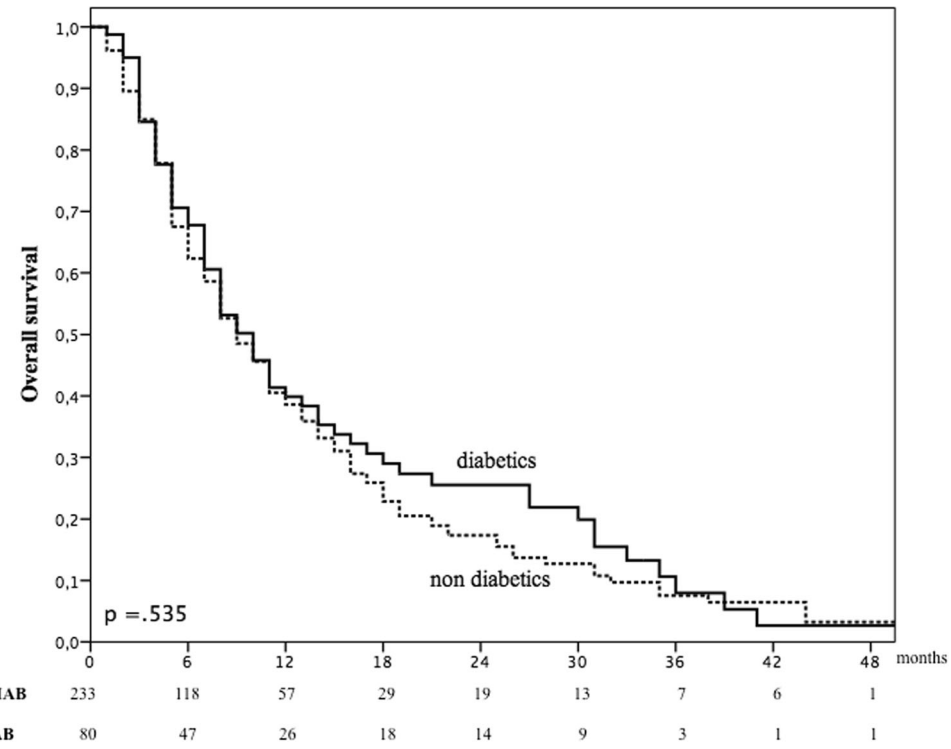

Fig. 1 Median overall survival in diabetic and nondiabetic patients

Table 3 Radiological response at 3 months in diabetic and nondiabetic patients

Radiological response	NDIAB	DIAB
Progression	41 (28.5 %)	9 (16.4 %)
Stable	65 (45.1 %)	26 (47.3 %)
Partial response	33 (22.9 %)	19 (34.5 %)
Complete response	5 (3.5 %)	1 (1.8 %)

in the DIAB group. Cancer progression was observed in 107 among 233 patients and in 31 among 80, in the nDIAB and DIAB groups, respectively. Median TTP was 19 months (95%CI, 2.06-35.94) in the DIAB group and 9 months (95%CI, 6.51-11.49) in the nDIAB group ($P = .038$) (Fig. 2). In the DIAB group, median TTP was 16 months in insulin-treated patients and 27 months in patients treated with oral hypoglycemic agents.

4 Discussion

This is the first study that evaluated the interaction between diabetes and sorafenib treatment in a large cohort of HCC patients.

Type 2 diabetes increases the risk of HCC occurrence by two to four fold [6, 7]. Liver steatosis and steatohepatitis often observed in diabetics may be a cause for it. However, type 2 diabetes may also stimulate cancer development and progression by hyperglicemia and hyperinsulinemia. According to the Warburg hypothesis, hyperglicemia favours glycolisis that is a main energy producing process in many cancer cells [24]. Hyperinsulinemia is a risk factor for the development of cancer [25, 26]. Insulin produced by pancreatic cells through portal circulation reaches the liver and, therefore, is exposed to very high concentrations of this hormone [27]. Insulin and insulin-like growth factor receptors are expressed on the surface of most cancer cells. Insulin receptor is expressed mainly as A isoform. Both receptors when activated may enhance cancer cell proliferation, metastasis, and inhibit apoptosis. In particular, the activation of A isoform insulin receptors may enhance more cell survival and proliferation than glucose uptake [28]. Another mechanism may be the reduced hepatic synthesis of insulin growth factor-binding protein-1, resulting in increased bioavailability of insulin-like growth factor-1 which leads to cellular proliferation promotion and apoptosis inhibition [29].

The risk of cancer occurrence is higher in patients treated with insulin or sulfonylureas, whereas it is reduced with the use of metformin [8, 30, 31]. Some epidemiologic studies and basic science suggests an association between metformin use and lower cancer risk in diabetic patients, in particular it is associated with lower incidence and mortality for all cancers. Pathophysiological mechanisms of this significant risk have been proposed, but they are still incompletely defined. Metformin has a potential anti-cancer effect by activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) in addition to alleviating hyperinsulinemia and hyperglycemia. [32]. Metformin has also a direct effect on $CD8^+$ tumor-infiltrating lymphocytes protecting them from

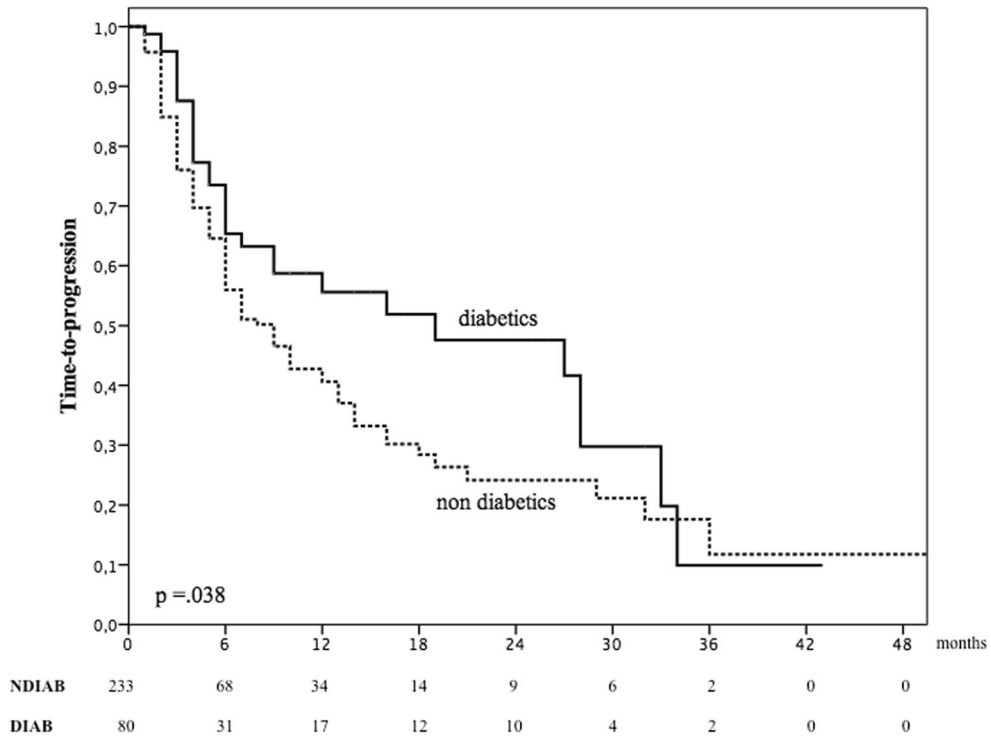

Fig. 2 Time-to-progression in diabetic and nondiabetic patients

Table 4 Mechanisms potentially involved in diabetes amelioration during tyrosine kinase inhibitors treatment

Target	Effects
VEGF-R	capillary regression in pancreatic islets [36]
IGF-1, PDGF-R	insulin resistance reduction
c-Abl, MAPK JNK, NF-kB	decreased apoptosis of beta-cells [37]
c-Kit	decreased inflammatory response

apoptosis and counteracting immune exhaustion [33]. Furthermore, metformin seems to inhibit cancer cell proliferation acting as a negative regulator of mTOR [34].

In patients not treated with sorafenib, some studies have shown that diabetes may worsen the outcomes of HCC patients [10, 35].

Tyrosine kinase inhibitors can affect the insulin signalling pathway reducing the mitogenic effect and improving glycemic control in diabetics. This last effect was observed in 11 % of our patients. Potential mechanisms related to this effect are shown in Table 4. In a single patient a severe episode of hypoglicemia occurred. These findings suggest that patients with diabetes who are treated with sorafenib should be cautiously monitored.

The main aim of the study was to test if systemic treatment was as effective and safe in patients with unresectable HCC and type 2 diabetes as compared to patients without diabetes.

Sorafenib therapy in diabetic patients was safe. Adverse events occurred with comparable frequency in DIAB and nDIAB patients, except for skin rash that was observed more often in the DIAB group. Median daily dose was comparable between the DIAB and nDIAB groups. Also temporary or definitive discontinuation of sorafenib due to adverse effects was registered with the same rate in the two groups. Overall survival was similar between DIAB and nDIAB groups.

Among secondary outcomes, 3-month radiological response evaluation showed a lightly higher rate of DCR in DIAB than in nDIAB patients, but the difference did not reach statistical significance.

Unexpectedly, a longer TTP in the DIAB group as compared to the nDIAB group (19 vs 9 months, $P = .038$) was observed. This finding needs to be evaluated in prospective studies. The TTP was longer in DIAB patients treated with oral hypoglycemic agents as compared to those treated with exogenous insulin (27 vs 16 months). These findings contrast with the results of another study showing a shorter progression-free survival and OS in sorafenib-treated patients taking metformin as compared to insulin-treated patients [38]. Definitive conclusions cannot be drawn due to the low number of patients, although previous studies on other cancer types showed that metformin increased the response to chemotherapy and decreased the occurrence of metastasis [39–42]. Furthermore, in a recent study on metastatic renal carcinoma, for patients treated with sunitinib, the OS was longer in diabetics taking metformin [43].

In conclusion, sorafenib was as safe as effective in DIAB and in nDIAB patients. The longer TTP observed in DIAB as compared to nDIAB patients might suggest a better anticancer effect of sorafenib in patients with diabetes. Also, the better TTP in DIAB treated with oral therapy as compared to those receiving insulin is interesting and concordant with previous studies on other cancer types. However, due to the retrospective design of the analysis, these last findings need to be tested in prospective controlled studies.

Acknowledgments

Author Contributions
- Study concept and design: GGDC, RT.
- Acquisition of data: RT, GC, LF, LA.
- Analysis and interpretation of data: GGDC, FM, NC.
- Drafting of the manuscript: GGDC, MG.
- Critical revision of the manuscript for important intellectual content: GGDC, MG, RT.
- Statistical analysis: GGDC.
- Study supervision: GGDC.

All authors read and approved the final manuscript.

Compliance with Ethical Standards

Funding None.

Conflict of Interest Giovan Giuseppe Di Costanzo, Raffaella Tortora, Filomena Morisco, Luigi Addario, Maria Guarino, Gabriella Cordone, Luigia Falco, and Nicola Caporaso declare no conflict of interest.

References

1. GLOBOCAN Cancer incidence and mortality worldwide. International Agency for Research on Cancer. World Health Organization, 2012. http://globocan.iarc.fr.
2. Benvegnù L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. Gut. 2004;53:744–9.
3. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology. 2006;43:1303–10.
4. Ascha MS, Hanouneh IA, Lopez R, Tamimi TAR, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010;51:1972–8.
5. Jinjuvadia R, Patel S, Liangpunsakul S. The association between metabolic syndrome and hepatocellular carcinoma: systemic review and meta-analysis. J Clin Gastroenterol. 2014;48(2):172–7.
6. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126:460–8.
7. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the

United States: a population based case control study. Gut. 2005;54(4):533–9. doi:10.1136/gut.2004.052167.
8. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer. 2010;116:1938–46.
9. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. Cancer. 2004;101:1009–17.
10. Toyoda H, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, et al. Impact of diabetes mellitus on the prognosis of patients with hepatocellular carcinoma. Cancer. 2001;91:957–63.
11. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 2001;285:885–92.
12. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21:433–40.
13. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004;159:1160–7.
14. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. Hepatology. 1994;20:119–25.
15. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208–36.
16. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
17. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol. 2005;2:48–53.
18. Van de Poll-Franse LV, Houterman S, Janssen-Heijnen MLG, Dercksen MW, Coebergh JWW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120:1986–92.
19. Imarisio I, Paglino C, Ganini C, Magnani L, Caccialanza R, Porta C. The effect of sorafenib treatment on the diabetic status of patients with renal cell or hepatocellular carcinoma. Future Oncol. 2012;8(8):1051–7.
20. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
21. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
22. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl):S8–S16.
23. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
24. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324:1029–33.
25. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, de Jong-Bakker M, Nooijen WJ. Insulin resistance and breast-cancer risk. Int J Cancer. 1992;52:511–16.
26. Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe KD, Swanson GM, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer. 1999;80:1830–7.
27. Ferrannini E, Cobelli C. The kinetics of insulin in man. II. Role of the liver. Diabetes Metab Rev. 1987;3:3365–97.
28. Denley A, Carroll JM, Brierley GV, Cosgrove L, Wallace J, Forbes B, et al. Differential activation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors. Mol Cell Biol. 2007;27:3569–77.
29. Moore MA, Park CB, Tsuda H. Implications of the hyperinsulinaemia-diabetes-cancer link for preventive efforts. Eur J Cancer Prev. 1998;7:89–107.
30. Donadon V, Balbi M, Ghersetti M, Grazioli S, Perciaccante A, Della Valentina G, et al. Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. World J Gastroenterol. 2009;15:2506–11.
31. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006;29:254–8.
32. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012;7:e33411.
33. Eikawa S, Nishida M, Mizukamia S, Yamazakia C, Nakayamab E, Udonoa H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. PNAS. 2015;112:1809–14.
34. Sahra IB, Regazzetti C, Robert G, Laurent K, Le Marchand-Brustel Y, Auberger P, et al. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1. Cancer Res. 2011;71:4366–72.
35. Huo T-I, Lui W-Y, Huang Y-H, Chau GY, Wu JC, Lee PC, et al. Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. Am J Gastroenterol. 2003;98:2293–8.
36. Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, et al. VEGF-dependant plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol. 2006;290:H560–76.
37. Veneri D, Franchini M, Bonora E. Imatinib and regression of type 2 diabetes. N Engl J Med. 2005;10:1049–50.
38. Casadei Gardini A, Marisi G, Scarpi E, Scartozzi M, Faloppi L, Silvestris N, et al. Effects of metformin on clinical outcome in diabetic patients with advanced HCC receiving sorafenib. Expert Opin Pharmacother. 2015;16:2719–25.
39. Li D. Metformin as an antitumor agent in cancer prevention and treatment. J Diabetes. 2001;3(4):320–7.
40. Rocha GZ, Dias MM, Ropelle ER, Osório-Costa F, Rossato FA, Vercesi AE, et al. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. Clin Cancer Res. 2011;17(12):3993–4005.
41. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? Mol Cancer Ther. 2010;9(5):1092–9.
42. Rattan R, Ali Fehmi R, Munkarah A. Metformin: an emerging new therapeutic option for targeting cancer stem cells and metastasis. J Oncol. 2012;2012:928127.
43. Keizman D, Ish-Shalom M, Sella A, Gottfried M, Maimon N, Peer A, et al. Metformin use and outcome of sunitinib treatment in patients with diabetes and metastatic renal cell carcinoma. Clin Genitourin Cancer. 2016;S1558–7673(16):30102–1.