The Oncologist®
Hepatobiliary

Early Skin Toxicity as a Predictive Factor for Tumor Control in Hepatocellular Carcinoma Patients Treated with Sorafenib

Bruno Vincenzi,[a] Daniele Santini,[a] Antonio Russo,[b] Raffaele Addeo,[c] Francesco Giuliani,[d] Liliana Montella,[c] Sergio Rizzo,[b] Olga Venditti,[a] Anna Maria Frezza,[a] Michele Caraglia,[e] Giuseppe Colucci,[d] Salvatore Del Prete,[c] Giuseppe Tonini[a]

[a]Medical Oncology, University Campus Bio-Medico, Rome, Italy; [b]Section of Medical Oncology, Department of Surgical and Oncological Sciences, Università di Palermo, Palermo, Italy; [c]Oncology Unit, S. Giovanni di Dio Hospital, Naples, Italy; [d]Medical and Experimental Oncology Unit, Oncology Institute, Bari, Italy; [e]Department of Biochemistry and Biophysics, Second University of Naples, Naples, Italy

Key Words. Sorafenib • Hepatocellular carcinoma • Skin rash

Disclosures: Bruno Vincenzi: None; **Daniele Santini:** None; **Antonio Russo:** None; **Raffaele Addeo:** None; **Francesco Giuliani:** None; **Liliana Montella:** None; **Sergio Rizzo:** None; **Olga Venditti:** None; **Anna Maria Frezza:** None; **Michele Caraglia:** None; **Giuseppe Colucci:** None; **Salvatore Del Prete:** None; **Giuseppe Tonini:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors or independent peer reviewers.

Abstract

Introduction. **Sorafenib is an oral multikinase inhibitor that targets Raf kinase and receptor tyrosine kinases and has led to a longer median overall survival (OS) time and time to progression (TTP) in patients with advanced hepatocellular carcinoma (HCC). This study was conducted to assess the link between the antitumor efficacy of sorafenib and its early cutaneous side effects in advanced HCC patients.**

Materials and Methods. **All patients received 800 mg daily of sorafenib until progression or unacceptable toxicities. We retrospectively analyzed the incidence of rash and hand–foot skin reactions (HFSR) during the first month of treatment, comparing tumor control (partial response plus stable disease) and TTP.**

Results. **Sixty-five HCC patients treated with sorafenib were included in this analysis: 47 (73.3%) received sorafenib after failure of some local treatment, whereas 18 (27.7%) received it as first-line treatment. Twenty-nine patients developed at least grade 1 skin toxicity (rash, 13; HFSR, 16). In patients who developed skin toxicity, the tumor control rate was 48.3%, versus 19.4% in patients without cutaneous side effects. The median TTP was 8.1 months in the group of patients with skin toxicity versus 4.0 months in those without skin toxicity. This difference was also statistically significant on multivariate analysis. A borderline statistically significant difference was also observed in terms of OS in patients with early skin toxicity.**

Conclusions. **Skin toxicity should be closely monitored in HCC patients treated with sorafenib in relation to its potential role as a surrogate marker of efficacy.** ***The Oncologist*** 2010;15:85–92

Correspondence: Antonio Russo, M.D., Ph.D., Department of Surgical and Oncological Sciences, Section of Medical Oncology; Università di Palermo, Palermo, Italy, Via del Vespro 127, 90127 Palermo, Italy. Telephone: 39-091-6552500; Fax: 39-091-6554529; e-mail: lab-oncobiologia@usa.net Received July 8, 2009; accepted for publication December 7, 2009; first published online in ***The Oncologist Express*** on January 5, 2010. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2009-0143

Introduction

Nowadays, hepatocellular carcinoma (HCC) treatment still represents a considerable challenge. Surgery, including liver transplantation, is the most important therapeutic option for patients with this disease, but unfortunately it can be considered a possible approach only in patients with a good performance status and early-stage HCC. Most of the patients affected by HCC still have a poor prognosis, and new therapeutical possibilities are needed to face this aggressive disease.

Sorafenib is an oral multikinase inhibitor that has shown potent in vitro activity by targeting the Raf/mitogen-activated protein kinase/extracellular signal–related kinase signaling pathway. Sorafenib inhibits cell surface tyrosine kinase receptors (vascular endothelial growth factor receptor [VEGFR]-2, VEGFR-3, and platelet-derived growth factor receptor β) and downstream intracellular serine/threonine kinases (Raf-1, wild-type B-Raf, and mutant B-Raf) involved in both tumor cell proliferation and tumor angiogenesis [1]. Sorafenib first came to attention in early clinical trials enrolling patients with refractory solid tumors. It is approved today for the treatment of advanced renal cancer in patients previously treated with interferon-α or interleukin-2, or when these first-line therapies are considered unsuitable. More recently, sorafenib was found to have significant clinical activity against HCC in phase II and phase III studies [2, 3], in which it was found to lead to a longer median survival time and time to radiologic progression when compared with placebo. As well as significant activity, sorafenib is characterized by a good tolerability profile. The main side effects associated with sorafenib are diarrhea, nausea, fatigue, hypertension, and dermatological toxicities including alopecia, stomatitis, erythema, and hand–foot skin reaction (HFSR).

HFSR (Table 1) is a cutaneous reaction characterized by erythema, numbness, tingling, and dysesthesia or paresthesia, particularly on the palms and soles. Swelling of the skin, desquamation, ulceration, or blistering may occur in advanced cases [4]. HFSR is often also referred to as hand–foot syndrome (HFS) and palmar–plantar erythrodysesthesia. Although the literature suggests some differences between HFSR and HFS [5, 6], up to today the evidence does not seem to be sufficiently convincing to make this distinction. In this manuscript we have opted to refer to the toxicity as HFSR.

The aim of the present retrospective study was to explore the potential association between HFSR and efficacy in HCC patients treated with sorafenib.

Table 1. Hand–foot skin reaction

Grade 0	None
Grade 1	• Numbness • Unpleasant sensations when touching ordinary things • Burning or prickling feeling • Tingling • Painless swelling • Redness or discomfort of hands or feet
Grade 2	One or more of the following: • Painful redness • Swelling • Skin thickening of the hands or feet Symptoms create discomfort but do not affect the patient's normal daily activities
Grade 3	One or more of the following: • Scaling or shedding of skin • Open sores • Blistering • Skin thickening • Severe pain of the hands and feet Severe discomfort that causes the patient to be unable to work or perform daily activities

Materials and Methods

Patients with a histologically confirmed diagnosis of HCC and advanced disease not suitable for locoregional treatments were analyzed. Other inclusion criteria were: age >18 years; performance status score of 0 or 1; Child–Pugh (CP) class A or B; life expectancy ≥12 weeks; and adequate hematologic, hepatic, and renal function. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection status at baseline was collected from medical history or laboratory tests.

Standard criteria for anticancer treatment suitability for all patients were used. In particular, renal function was evaluated, and only patients within the normal range (serum creatinine, 0.8–1.44 mg/dl) were included. Thyroid function was also studied.

Patients were considered ineligible for this analysis if they had reported fever (body temperature >38.0°C) during the last week before study entry, in order to avoid confounding factors influencing the presence and the severity of side effects, or had received any radiotherapy, chemotherapy, immunotherapy, or growth factors during the last 4 weeks before the analysis. Patients recently (<1 week) or simultaneously treated with chronic steroid-based therapy, affected by acute or chronic infection or inflammatory diseases or with a previous medical history suggestive of chronic rashes were considered ineligible for the study. We compared tumor control (partial response plus stable disease), time to progression (TTP), and overall survival (OS) in patients who developed at least grade 1 rash or HFSR and

patients who did not present any reaction. The starting date of the study was November 2007 and the cutoff point for survival data was August 2009.

Treatment Plan and Toxicity Evaluation

Patients received sorafenib (800 mg), and treatment was continued until disease progression or unacceptable drug-related toxicities. Dose reduction was allowed for unacceptable toxicities, as previously reported [7]. No corticosteroids were routinely administered, and those patients treated with steroids for any reason were excluded.

Tumor response was evaluated every 8 weeks by the use of consistent imaging techniques (computed tomography or magnetic resonance imaging). Assessment was performed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients included in this analysis were categorized on the basis of their best tumor response as either responders (patients showing a complete or partial response) or nonresponders (patients with stable or progressive disease or whose disease status was not assessable). Adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 3. Skin toxicity was evaluated and scored by two independent physicians who separately examined each patient with a full skin exam. Standardization of skin toxicity was achieved by the use of the NCI-CTCAE (version 3), as previously reported.

Patients were divided into two groups: patients who experimented at least a grade 1 skin toxicity (considered as rash and/or HFSR) within the first month of treatment and those who did not.

Statistical Analysis

Data on treatment activity in the two different groups were analyzed considering tumor control, defined as the percentage of patients who had a best response of complete response, partial response, or stable disease (according to the RECIST) that was maintained for at least 28 days.

TTP was calculated as the period from the beginning of treatment to the date of the first observation of disease progression after the start of treatment or the most recent tumor assessment. TTP was determined by the Kaplan–Meier product-limit method [8].

Stratified permutation tests were carried out to explore the association between tumor response and early skin toxicity. Moreover, the differences in terms of TTP according to the presence and severity of skin toxicity were evaluated by the log-rank test [9]. The Cox proportional hazards model was applied to the multivariate survival analysis [10].

The cutoff point for survival data was August 2009. SPSS software (version 17.00, SPSS, Inc., Chicago, IL) was used for the statistical analysis. A p-value $< .05$ was considered to indicate statistical significance.

Results

Patient Features

We included, in the present analysis, 65 HCC patients (male/female, 42/23) treated with sorafenib monotherapy. The median age was 69 years (range, 43–81). Forty-seven patients (72.3%) received sorafenib after failure of local treatment (percutaneous ethanol injection, local ablation therapy such as microwave or radiofrequency ablation, transcatheter arterial chemoembolization [TACE], and hepatectomy) whereas 18 patients (27.7%) received it first line. In 48 patients (73.8%), HCC was limited to the liver, and in 17 patients (26.2%) HCC involved other organs. Moreover, 41 patients (63.1%) showed elevated circulating α-fetoprotein levels whereas 24 patients (36.9%) did not. In 52 patients, a viral etiology (HCV or HBV) was confirmed by standard screening tests. All patients were classified as CP class A or B. Regarding skin toxicity, 29 patients developed at least grade 1 skin toxicity within the first month of sorafenib treatment (rash, 13; HFSR, 16). No patient developed rash after the first month of treatment, and only three patients developed HFSR after this period. The incidence of skin toxicity did not seem to depend upon either the different etiologies of liver disease or CP class. Only one patient in the group of patients with skin toxicity showed a radiological partial response, versus none in the group without skin toxicity. This difference was not statistically significant. The distribution of patients who needed a sorafenib dose reduction was similar between the group with skin toxicity and the group without skin toxicity (20.7% versus 19.4%). Furthermore, in terms of dose delay, no statistically significant difference was detected between the two groups (34.5% versus 38.9%). The most common adverse events that led to drug dose reduction and dose delay were gastrointestinal side effects followed by liver dysfunction.

The main characteristics of patients are reported in Table 2.

Univariate Analysis

In patients who developed early skin toxicity, tumor control was obtained in 14 patients (48.3%), versus only seven patients (19.4%) in the group without skin toxicity ($p = .028$).

The median TTP was 8.1 months (95% confidence interval [CI], 6.2–12.1) in the group of patients with early skin toxicity, versus 4.0 months (95% CI, 2.2–7.0) in patients who did not develop skin toxicity ($p = .006$; see Fig.

Table 2. Patient features

Feature	*n*	%
n of included patients	65	100%
Median age (range)	69 yrs (43–81 yrs)	–
Gender		
Male	42	64.6%
Female	23	35.4%
Child-Pugh class		
A	44	67.7%
B	21	32.3%
HCC etiology		
HCV	37	56.9%
HBV	15	23.1%
Unknown (common virus screening negative)	13	20.0%
Previous treatment		
Yes	47	72.3%
No	18	27.7%
Elevated α-fetoprotein		
Yes	41	63.1%
No	24	36.9%
Disease extension		
Liver only	48	73.8%
Metastatic disease	17	26.2%
Portal vein thrombosis		
Yes	22	33.8%
No	43	66.2%
Total bilirubin level		
<2 mg/dl	43	66.2%
≥2 mg/dl	22	33.8%
Presence of ascites		
Yes	17	26.2%
No	48	73.8%
ECOG PS score		
0–1	41	63.1%
2	24	36.9%
Albumin level		
<3.5 mg/dl	39	60%
≥3.5 mg/dl	26	40%

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

1). A borderline statistically significant difference ($p = .09$) was also observed in terms of the OS time in patients with early skin toxicity, 11.2 months, versus 7.8 months in patients without skin toxicity. Among the other clinical factors that could have a predictive value in this population, the following were analyzed: CP class, previous local treatment, elevated circulating α-fetoprotein level, local or metastatic disease, and the presence or absence of portal vein thrombosis. Among these, only disease extension ($p = .01$) and previous (local) treatments ($p = .02$) were demonstrated to be predictive of efficacy with statistical significance, as reported in Table 3. No difference in terms of efficacy was detected in relation to the type of early skin toxicity (rash versus HFSR).

Multivariate Analysis of Survival

According to a multivariate analysis of TTP, the development of early skin toxicity maintained statistical significance whereas the other clinical prognostic factors lost their statistical significance. In detail, the calculated relative risk for progression in the group of patients with early skin toxicity was 0.412 (95% CI, 0.176–0.820), with a *p*-value of .02. The relative risk for progression for the group of previously untreated patients was 0.822 (95% CI, 0.710–1.920), when compared with previously treated patients ($p = .802$), whereas the relative risk for progression in patients with only liver involvement was 0.450 (95% CI, 0.415–1.067), when compared with the group of patients with systemic disease ($p = .170$).

All these data are reported in Table 4.

Discussion

HCC is still considered today to be a highly aggressive disease. It has been estimated that 22,620 new cases of HCC or intrahepatic bile duct cancer were diagnosed in 2009 in the U.S., with approximately 18,160 deaths [11]. In western countries, chronic HBV infection is the main risk factor, whereas in Asia and Africa chronic HCV has been proven to be the most relevant one. Other causes of HCC include alcoholic liver cirrhosis and aflatoxin exposure [12].

The treatment of HCC represents a challenge for oncologists, considering its increase in incidence and the poor prognosis of the disease.

Partial hepatectomy or transplantation are the only curative treatments, with a 5-year OS rate of about 50%–70% [13]. Transplantation is an attractive option for patients affected by early-stage HCC with moderate to severe cirrhosis (CP class B or C), because it removes detectable and undetectable lesions, cures the underlining cirrhosis, and is not associated with complications resulting from the future liver remnant. Partial hepatectomy is generally recognized as the best choice in CP class A patients affected by HCC, although there are no studies that directly compare the effectiveness of this approach with that of liver transplant in this class of patients, whose treatment still remains controversial [14]. In patients not suitable for surgical treatment,

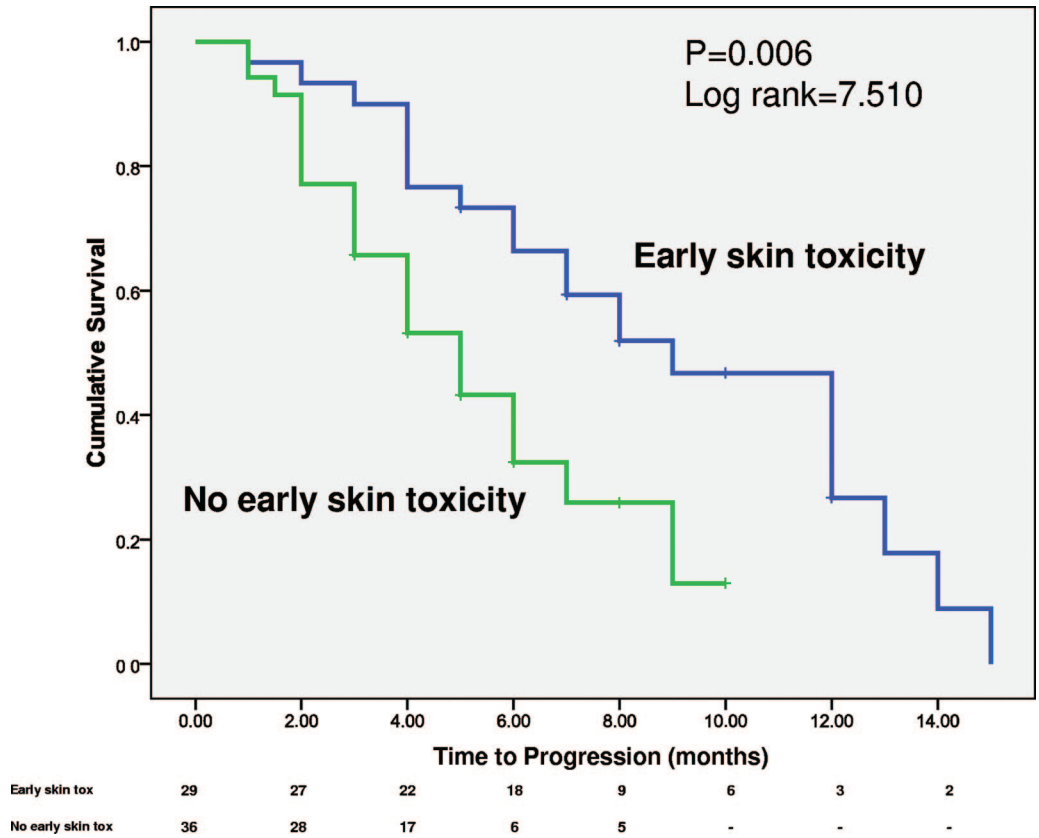

Figure 1. Kaplan–Meier survival plot for time to progression according to early skin toxicity.

chemoembolization and/or ablative procedures have been suggested on the basis of a meta-analysis demonstrating a survival advantage [15]. Consistent with these recommendations, two well-designed, randomized trials have shown that chemoembolization has a positive impact on survival. Lo et al. [16] randomized patients to receive supportive care or chemoembolization, finding patient survival rates of 57%, 31%, and 26% in the chemoembolization group versus 32%, 11%, and 3% in the control group at 1, 2, and 3 years, respectively. A second randomized trial, by Llovet et al. [17], randomized 112 patients to transarterial embolization (TAE), TACE, or supportive care, confirming the clear survival benefit of TACE and TAE (1- and 2-year survival rates of 82% and 63% for TACE versus 63% and 27% for the supportive care group, respectively).

Recently, sorafenib was approved as an appropriate treatment in patients with advanced HCC: the Sorafenib Hepatocarcinoma Assessment Randomized Protocol (SHARP) study pointed out how the median survival time and time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those in the placebo group. In the SHARP study, among 602 patients (299 receiving sorafenib and 303 receiving placebo), the median OS time was 10.7 months in the sorafenib group, compared with 7.9 months in the placebo group. The median time to symptomatic progression was 4.1 months in the sorafenib group, as compared with 4.9 months in the placebo group. The median time to radiologic progression was 5.5 months in the sorafenib group, as compared with 2.8 months in the placebo group [18]. These previous data were recently confirmed by a phase III study on HCC in an Asia-Pacific population [19].

Beside its activity, sorafenib seems to be well tolerated: the principal side effects reported are diarrhea, nausea, fatigue, hypertension, and dermatological toxicities, including HFSR, alopecia, stomatitis, erythema, and hemorrhage.

The severity of HFSR is dose related, and depends on the duration, dosage, and accumulation of the drug [20]. Histologically, HFSR is characterized by thick, well-defined hyperkeratotic lesions frequently affecting digit flexural locations: this peculiar characteristic led to the term HFSR. Although sorafenib-induced HFSR is usually not a life-threatening side effect, it affects quality of life in a significant manner and can be complicated by infection, pain, and limitation of activities of daily living. In addition, it represents a dose-limiting toxicity, and may compromise the efficacy of the treatment because of dose reduction. A randomized, placebo-controlled, phase III trial called Treat-

Table 3. Univariate analysis of TTP

Feature	Median TTP (95% CI) in mos	*p*-value
Early skin toxicity		
Yes	8.1 (6.2–12.1)	**.006**
No	4.0 (2.2–7.0)	
Child-Pugh class		
A	8.1 (5.1–10.2)	.129
B	5.7 (4.2–8.3)	
Previous treatment		
Yes	4.1 (2.3–7.2)	**.020**
No	8.3 (6.1–10.9)	
Elevated α-fetoprotein		
Yes	6.6 (3.2–8.9)	.810
No	7.1 (4.0–10.5)	
Disease extension		
Metastatic disease	4.2 (2.7–7.1)	**.012**
Liver only	9.0 (5.9–10.1)	
Portal vein thrombosis		
Yes	5.9 (3.9–7.2)	.431
No	7.6 (5.1–10.1)	

p-values in bold are statistically significant.
Abbreviations: CI, confidence interval; TTP, time to progression.

Table 4. Multivariate analysis of TTP

Feature	Relative risk for progression	95% CI	*p*-value
Early skin toxicity			
No	–	–	**.02**
Yes	0.412	0.176–0.820	
Previous treatment			
Yes	–	–	.802
No	0.822	0.710–1.920	
Disease extension			
Metastatic disease	–	–	.170
Liver only	0.450	0.415–1.067	

p-value in bold is statistically significant.
Abbreviations: CI, confidence interval; TTP, time to progression.

ment Approaches in Renal Cancer Global Evaluation Trial, reported that HFS occurred in approximately 26.0% of patients. In that trial, dermatological toxicities were the most frequent cause of dose reduction (13%), interruption (21%), and discontinuation (10%) [21]. The exact mechanism by which sorafenib produces painful palm/sole blisters remains unclear, but the higher incidence and greater severity of rashes at higher doses suggest that it is not the result of an allergic reaction [22].

The acneiform rash (most often acne-like) usually occurs a few days after administration of sorafenib, and reaches a maximum after 2–3 weeks from the start of treatment. The characteristic rash is frequently detected on the face, neck and retroauricular area, scalp, and upper trunk.

The skin lesions consist of sometimes itchy, erythematous follicular papules that may evolve into pustules [23]. The pustules may flow into lakes of pus that evolve into yellow crusts [24]. Sometimes the facial lesions consist of diffuse erythema with follicular papulopustules and telangectasia resembling rosacea. In other cases, a seborrheic dermatitis-like picture is seen on the face when the pustules leave an erythema covered with small greasy squames. An increase in drug concentration in the rich capillary network at the thickened papillary dermis and resultant increased blood flow is one of the proposed mechanisms, because the palms, soles, and fingertips are areas of repeated friction, grasping, or trauma.

Much experience suggests a possible correlation between some toxicities related to monoclonal antibodies or small molecules and response. In advanced colorectal cancer, the acne-like rash induced by the epidermal growth factor receptor inhibitors cetuximab and panitumumab has been proven to be related to a better outcome [25, 26]. Interestingly, among patients with bevacizumab-related hypertension, a significantly superior global clinical outcome was observed, particularly in terms of the response rate and TTP (response rate, 75% versus 32%; $p = .04$. TTP, 14.5 months versus 3.1 months; $p = .04$). No statistically significant difference was noted for the median OS time. These results indicate that the development of grade 2–3 hypertension in patients treated with bevacizumab may be an indicator of antitumor activity [27]. These data were confirmed by the following observations, according to which the occurrence of hypertension is predictive of a clinical benefit (objective response and stable disease) in the treatment of metastatic renal cell cancer regardless of the antiangiogenic used (sunitinib, sorafenib, or bevacizumab) and regardless of the line of treatment (first or second) [28]. In contrast, there does not seem to be any relationship between hypertension and the outcome of patients affected by glioblastoma treated with bevacizumab [29].

With the aim to evaluate the role of early cutaneous toxicity as a surrogate marker of efficacy, we performed a retrospective analysis in advanced HCC patients treated with the multikinase inhibitor sorafenib.

The results of our analysis showed a positive correlation

between the early incidence of skin reactions and tumor control and TTP. Our data seem to confirm the role of early cutaneous toxicity as a surrogate marker of efficacy similar to those observed in colorectal cancer [30].

Our results also suggest that the appearance of skin toxicity during therapy may indicate antitumor activity: the identification of a reliable marker of antitumor efficacy could be extremely useful in clinical practice, in order to understand the real efficacy of the therapy and, if necessary, change the treatment strategy early on.

In particular, the results of our study show a relationship between the development of a rash during sorafenib therapy and longer TTP and better disease control. A borderline statistically significant difference was also observed in terms of OS. The data reported are limited by the retrospective nature of the study and its small size.

Conclusion

In our experience, a significantly superior global clinical outcome was found in patients affected by HCC and treated with sorafenib who developed a related early skin toxicity.

These results, together with other observations reported in similar studies employing different biological agents, suggest that the identification of a reliable clinical factor such as skin rash developing during different treatments may constitute an early indicator of antitumor activity. In contrast, the absence of this side effect might suggest a lack of antitumor activity of the drug and perhaps suggest a change in therapy.

Despite these findings, it is right and proper to remember that HFSR remains a serious toxicity that needs to be avoided or treated appropriately. The clinical manifestation and the pathogenesis of HFSR should be evaluated through collaboration with dermatologists, and a multidisciplinary approach would help to gain a better understanding and treatment of this phenomenon.

Author Contributions

Conception/Design: Liliana Montella, Michele Caraglia, Salvatore Del Prete, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Raffaele Addeo, Sergio Rizzo, Giuseppe Tonini

Provision of study material or patients: Liliana Montella, Olga Venditti, Francesco Giuliani, Michele Caraglia, Anna Maria Frezza, Salvatore Del Prete, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Raffaele Addeo, Giuseppe Tonini

Collection and/or assembly of data: Liliana Montella, Olga Venditti, Francesco Giuliani, Michele Caraglia, Anna Maria Frezza, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Sergio Rizzo, Giuseppe Tonini

Data analysis and interpretation: Antonio Russo, Olga Venditti, Michele Caraglia, Anna Maria Frezza, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Sergio Rizzo, Giuseppe Tonini

Manuscript writing: Antonio Russo, Michele Caraglia, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Sergio Rizzo, Giuseppe Tonini

Final approval of manuscript: Antonio Russo, Liliana Montella, Olga Venditti, Francesco Giuliani, Michele Caraglia, Anna Maria Frezza, Salvatore Del Prete, Giuseppe Colucci, Bruno Vincenzi, Daniele Santini, Raffaele Addeo, Sergio Rizzo, Giuseppe Tonini

References

1 Wilhelm SM, Carter C, Tang L et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099–7109.

2 Moreno-Aspitia A, Morton RF, Hillman DW et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol 2009;27:11–15.

3 Abou-Alfa GK, Schwartz L, Ricci S et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24: 4293–4300.

4 Chu D, Lacouture ME, Fillos T et al. Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis. Acta Oncol 2008;47: 176–186.

5 Beldner M, Jacobson M, Burges GE et al. Localized palmar-plantar epidermal hyperplasia: A previously undefined dermatologic toxicity to sorafenib. ***The Oncologist*** 2007;12:1178–1182.

6 Robert C, Soria JC, Spatz A et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol 2005;6:491–500.

7 Lee MW, Seo CW, Kim SW et al. Cutaneous side effects in non-small cell lung cancer patients treated with Iressa (ZD1839), an inhibitor of epidermal growth factor. Acta Derm Venereol 2004;84:23–26.

8 Kaplan E, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.

9 Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977;35:1–39.

10 Cox DR. Regression models and life tables. J R Stat Soc B 1972;34 187–220.

11 Jemal A, Siegel R, Ward E et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–249.

12 Addeo R, Caraglia M, Del Prete S. Highlights of regional meeting of Italian Southern Oncological Group (GOIM): Focus on hepatocellular carcinoma: Biological and clinical background, therapeutic guide-lines and perspectives. 7 November 2008, Naples, Italy. Expert Opin Investig Drugs 2009; 18:373–378.

13 Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.

14 Benson AB, Abrams TA, Ben-Josef E et al. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers, Version I. Fort Washington, PA: National Comprehensive Cancer Network, 2010:1–59.

15 Lopez PM, Villanueva A, Llovet JM. Systematic review: Evidence-based management of hepatocellular carcinoma—an updated analysis of randomized controlled trials. Aliment Pharmacol Ther 2006;23:1535–1547.

16 Lo CM, Ngan H, Tso WK et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–1171.

17 Llovet JM, Real MI, Montaña X et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 2002;359: 1734–1739.

18 Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

19 Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.

20 Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer. J Clin Oncol 1998;16:3537–3541.

21 Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–134.

22 Strumberg D, Richly H, Hilger RA et al. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43–9006 in patients with advanced refractory solid tumors. J Clin Oncol 2005;23:965–972.

23 Busam KJ, Capodieci P, Motzer R et al. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. Br J Dermatol 2001;144:1169–1176.

24 Jacot W, Bessis D, Jorda E et al. Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. Br J Dermatol 2004;151:238–241.

25 Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–345.

26 Van Cutsem E, Lang I, D'haens G et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. J Clin Oncol 2008;26(15 suppl):2.

27 Scartozzi M, Galizia E, Chiorrini S et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol 2009;20:227–230.

28 Ravaud A, Sire M. Arterial hypertension and clinical benefit of sunitinib, sorafenib and bevacizumab in first and second-line treatment of metastatic renal cell cancer. Ann Oncol 2009;20:966–967; author reply 967.

29 Wick A, Schafer N, Dörner N et al. Arterial hypertension and bevacizumab treatment in glioblastoma: No correlation with clinical outcome. J Neurooncol 2009 Aug 29 [Epub ahead of print].

30 Saltz L, Kies M, Abbruzzese JL et al. The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies (abstract 817). Proc Am Soc Clin Oncol 2003; 22:204.