

Nexavar®-related adverse reactions: Calabrian (Italy) experience for sorafenib exposition in 2012

Felisa Cilurzo^{1,2}, Orietta Staltari^{1,2}, Marinella Patanè^{1,2}, Michele Ammendola³, Caterina Garaffo⁴, Eugenio Donato Di Paola^{1,2}

¹Department of Science of Health, School of Medicine, University of Catanzaro, ²Department of Science of Health, Pharmacovigilance's Centre Calabria Region, University Hospital Mater Domini, ³Department of Medical and Surgery Science, University of Catanzaro, Magna Graecia, Medical School, Catanzaro, ⁴Azienda Sanitaria Provinciale, Vibo Valentia, Italy

ABSTRACT

Hepatocellular carcinoma (HCC) remains a major global health problem and Calabria in the south of Italy is not an exception. Sorafenib is the first and only Food and Drug Administration approved drug for the treatment of advanced HCC and it is currently under intensive monitoring by the Health Authorities in Italy Agenzia Italiana del Farmaco. This general report has been developed with the aim of briefly reviewing the data found in the reports of adverse reactions (ADRs) collected in Calabria in 2012 for sorafenib treated patients. Extrapolated data have highlighted some differences between the adverse drug reactions reported in patients younger or older than 70 years and other important differences with the current approved leaflet. Several limitations might be present in data analysis from spontaneous reporting, however, the relevance of reporting ADRs (dermatitis, asthenia, vomiting, etc.) for the early identification of drug related signals has to be underlined.

Key words: Adverse effects, hepatocellular carcinoma, pharmacovigilance, safety, sorafenib

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a major global health problem.^[1] It is the fifth most common cancer in men, seventh in women and the third most common cause of cancer deaths world-wide.^[2] In 2008, approximately 749,000 new cases of HCC were diagnosed and 695,000 deaths were attributed to HCC. There is a distinct pattern of geographical distribution with the majority of the cases (85%) occurring in developing countries in East Asia and sub-Saharan Africa and lower

incidence rates in Australia, Northern Europe and America.^[3,4] The incidence of HCC in Italy is around 11 cases every 100,000 people: The highest in European countries.^[5]

The pathogenesis of HCC comprises a multistep progression involving chronic inflammation, hyperplasia, dysplasia and finally malignant transformation. The main risk factors for development of HCC are therefore related to the formation and progression of cirrhosis; in fact, cirrhosis is present in 80-90% of patients with HCC. Hepatitis B virus (HBV) is the predominant etiological agent accounting for approximately half of all cases of HCC. HBV infection is endemic in high incidence regions such as China and Africa. HBV also accounts for a large proportion of HCC cases among Asian Americans. Hepatitis C virus (HCV) confers a 15-20 fold increased risk of HCC and accounts for the majority of cases in Japan, United States and part of Europe. HCC related to HCV has become the fastest-rising cause of cancer-related death in the United States. Metabolic causes leading to non-alcoholic fatty liver

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Address for correspondence:

Eugenio Donato Di Paola, Department of Science of Health, School of Medicine, University of Catanzaro, Via T. Campanella, 115, 88100 Catanzaro, Italy. E-mail: dipaola@unicz.it

disease is also an increasing concern. The other risk factors for HCC can be classified as toxins (aflatoxin B1, alcohol), metabolic diseases, hereditary diseases (hemochromatosis) and immune related diseases (autoimmune hepatitis and primary biliary cirrhosis).^[5]

Despite decades of research in HCC, prognosis still remains poor. Only 20% of patients with HCC are amenable to curative strategies such as resection, transplantation or local therapy with radiofrequency ablation.^[6] Another 20% have multifocal lesions, for which loco-regional modalities such as transarterial chemoembolization^[8] or selective internal radiotherapy^[8] can be employed. The majority of patients are not candidates for curative treatment or loco-regional approaches and will receive systemic therapy if they have adequate hepatic reserve and good functional status.^[6] Due to underlying liver dysfunction, many patients do not receive any anti-cancer therapy and undergo palliative treatment for symptoms control with best have been made to molecularly characterize supportive care.

Substantial efforts have been made to do molecular characterization developing rationally targeted therapeutics in HCC and unlike other solid tumors, there are no oncogenic addiction loops that have successfully completed the journey from bench to bedside as validated therapeutic targets in HCC. Despite that, only one drug, sorafenib, has been approved by the Food and Drug Administration (FDA) for the treatment of advanced HCC, achieving modest objective response rates whilst still conferring an overall survival (OS) benefit.^[9] In this review, we characterize the adverse effect and incidence of sorafenib exposure in Calabria in the year 2012 based on age criteria.

CHEMOTHERAPY IN HCC

The scope of systemic chemotherapy is limited in HCC patients because of cirrhotic liver and potentially poor hepatic reserves. Specific complications of cirrhosis such as thrombocytopenia also compromise effective delivery of systemic chemotherapy. Several phase II trials with various chemotherapy agents such as Doxorubicin, Gemcitabine and Capecitabine have reported modest results. Among these agents, anthracyclines such as doxorubicin appear to have the highest efficacy, with a response rate of 20% and a median survival of 4 months.^[10]

SORAFENIB

Sorafenib is the first and only FDA approved drug for the treatment of advanced HCC. It inhibits multiple receptors, namely vascular endothelial growth factor 1-3, platelet-derived growth factor receptor-beta, c-KIT and Fms-related

tyrosine kinase-3.^[11] Sorafenib has been shown to inhibit angiogenesis, induce apoptosis and inhibit the mammalian target of rapamycin pathway in preclinical studies.^[11] FDA approval was based on the pivotal phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial. Llovet *et al.* randomized 602 patients (mainly from Europe) with unresectable advanced HCC with Child-Pugh 'A' score without prior systemic therapy to sorafenib 400 mg BD ($n = 299$) or placebo ($n = 303$).^[7] Compared to placebo, sorafenib significantly prolonged time to progression (TTP) from a median of 2.8 months to 5.5 months (hazards ratio [HR] = 0.58) and OS from a median of 7.9 months to 10.7 months (HR = 0.69; 95% confidence interval [CI] 0.55-0.87; $P < 0.001$). This randomized trial clearly established the survival benefit of sorafenib in advanced HCC. Notably, there was no difference in the median time to symptomatic progression (TTSP), a co-primary endpoint. A parallel study was performed in 271 Asian patients with advanced HCC by Cheng *et al.*, which also showed a statistically significant improvement of OS (HR = 0.68; 95% CI: 0.50-0.93; $P = 0.014$). However, outcomes in both arms were poorer with a median OS of 4.2 months in the placebo arm and 6.5 months with sorafenib therapy. Median TTP was 2.8 months in the sorafenib arm compared with 1.4 months in the placebo arm. Akin to the SHARP study, there was no significant difference in the TTSP.^[10] The shorter TTP and median OS in the Asian study was postulated to be due to the presence of more unfavorable prognostic factors including higher incidence of hepatitis B infections (73% vs. 12%), more advanced disease with a higher proportion of extrahepatic metastasis.

Common adverse reaction (ADR): Special warnings and precautions for use

Dermatological toxicities

Hand-foot skin reaction (palmar-plantar) and rash represent the most common ADRs with sorafenib. Rash and hand-foot skin reaction are usually Grades 1 and 2, according to the common toxicity criteria and generally appear during the first 6 weeks of treatment with sorafenib. The management of dermatologic toxicities include topical therapies for symptomatic relief, temporary interruption of sorafenib therapy and/or a change in its dosage or in severe/persistent cases, permanent discontinuation of sorafenib.

Hypertension

A higher incidence of arterial hypertension was observed in patients under sorafenib treatment. Hypertension was usually mild to moderate, occurred early and was amenable to treatment with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if necessary, in accordance with standard medical practice. In the case of severe or persistent hypertension or hypertensive crisis, despite being therapy-initiated hypertension, it is

recommended to consider permanent discontinuation of sorafenib administration.

Hemorrhage

The risk of bleeding may occur, following sorafenib administration. If a bleeding event necessitates medical intervention, it is recommended to consider the possibility of permanent discontinuation of sorafenib.

Cardiac ischemia and/or myocardial

In two previous studies,^[12] the incidence of heart attack or cardiac ischemia occurring during treatment was higher in the sorafenib group (from 2.7% to 4.9%) than in the placebo group (from 0.4% to 1.3%). The need for a temporary suspension or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

QT prolongation

It was shown that sorafenib prolongs the QT/QTc interval (also see below), which may lead to an increased risk of ventricular arrhythmias. Sorafenib should be used with caution in patients, who have or may develop QTc's prolongation, such as those with congenital long QT, those treated with a high cumulative dose of anthracyclines, patients taking certain antiarrhythmic agents or other medicines that may lead to QT prolongation (e.g., antidepressant drugs) and those with electrolyte abnormalities, such as hypokalemia, hypocalcemia or hypomagnesemia.

Gastrointestinal perforation

Gastrointestinal perforation is an uncommon event and has been reported in less than 1% of patients taking sorafenib. In some cases, this was not associated with evidence of intra-abdominal tumor. In case of gastrointestinal perforation administration of sorafenib must be discontinued.

Calabrian experience: General report on sorafenib safety Methods

For this work, reports of ADRs to sorafenib declared in Calabria during the year 2012 were collected. Evidently, this implies the presence of certain variability in the data considering the variability of the subjects. In fact, 29 reports were collected from subjects (5 women and 24 men) of different ages. At this point, in order to sort the data acquired, adverse event reports were divided to obtain the least possible deviation. For this reason, we first divided the scheduled patients into two subgroups: <70 years old and >70 years old (percentage calculation based on the number of subjects per group).

It is also important to underline the clear limitations of this study, regarding the little number of spontaneous ADR reported and last but not least, a lack of precision in completing the format of ADR reports.

RESULTS AND DISCUSSION

Figure 1 shows the relative percentage of incidence of ADRs in two different groups based on age. With the exception of some cases of untreated or treated hypertension (see precedent section), there are no reports of clinically significant concomitant diseases that could complicate the clinical picture of the patient. The doses administrated were always 800 mg/day, in coated tablets containing 200 mg of sorafenib.

As can be seen from the graph, diarrhea is present in 43% of those under 70, compared with 24% in the other group, as well as abdominal pain reported by a greater number of fewer than 70 than over 70. The opposite happens for dermatitis, 44% and 21% respectively for over and fewer than 70s. The discrepancy decreases to dysphonia and asthenia, although even in these cases the majority of those ADRs were observed in the under 70 group. Noteworthy, some ADRs were specifically and exclusively observed in over 70 such as fever, hypertension, tremors and vomiting; even though for some of the observed ADRs only one report was available.

According to the drug leaflet the most common adverse effects appear to be the palmar-plantar dermatitis, followed by hypertension. Gastrolesive-related problems are reported as rare adverse events. But in our studies most cases had abdominal pain or dermatitis in conjunction with gastrolesive-related problems.

The combination of other symptoms instead appears to be completely random, but this may be due to the small number of stakeholders. For this reason, this study will be implemented with the data of the current year.

Concomitant therapies

Only in two cases, the treated subject received concomitant therapy: The first of this with simvastatin (100 mg)

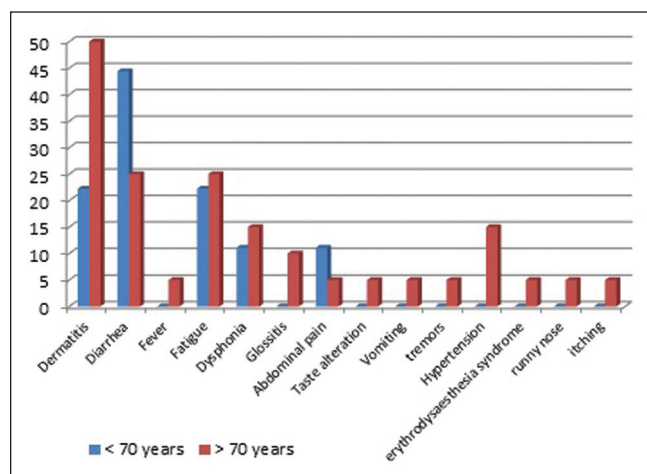


Figure 1: Percentage of occurrence of adverse reactions to different groups

and the drug combination irbesartan (300 mg) and hydrochlorothiazide (25 mg); the second with ramipril (2.5 mg) plus hydrochlorothiazide (12.5 mg). In all cases, it was people suffering from a form of unresectable HCC, in the range above the age of 70-year-old and male. These data, given the paucity, were not considered as a potential contributing cause of the ADRs observed; in fact, the drugs used in these few cases have no interference with sorafenib (especially with regard to hepatic metabolism) and ADRs indicated do not reflect the common framework of the two drugs.

CONCLUSIONS

Based on the reported data, it seems necessary to increase the monitoring of ADRs due to sorafenib and it is also important to get more information from adverse effect reports. These two limitations prevent us from giving a definitive value to our study, however, a discrepancy between what is reported in the package insert and our data might be relevant and undoubtedly deserves further confirmation by clinical studies. The main peculiarity is based on the variability of such ADRs in relation to patients' age. In conclusion, a greater number of available data and the clarity of these, especially on concomitant therapies, are necessary for a proper evaluation of the phenomenon. In any case, the usefulness of spontaneous ADR reporting can be confirmed and it should be always followed by proper clinical evaluation.

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