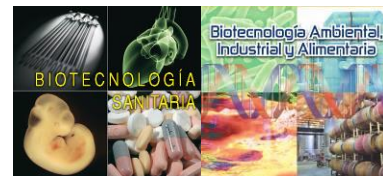


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## Relevance of p53 in the regulation of pro and antiapoptotic factors from the Bcl-2 family during the treatment with tyrosine kinase inhibitors



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### ABSTRACT

#### Motivation:

Liver cancer is the sixth most common cancer and the fourth most frequent cause of cancer-related death worldwide [1]. Nowadays, only one third of patients diagnosed with HCC are in the earliest BCLC 0-A stages, with a high proportion being in more advanced stages of the disease (BCLC B-C). Patients with the presence of poor prognostic factors such as vascular invasion, extrahepatic metastases and/or impaired hepatic function are considered in the advanced stage of the disease (BCLC C). Sorafenib is the standard of care for advanced HCC stage demonstrated in two large-scale trials [2]. Other drugs have been developed to increase the therapeutic arsenal of treatments. A phase III clinical trial comparing Lenvatinib and Sorafenib demonstrated that Lenvatinib was statistically non-inferior to Sorafenib in overall survival as a first-line treatment in patients with advanced HCC. Regorafenib and Cabozantinib have been shown to be effective as second-line therapy. [2]

#### Methods:

Sorafenib, Regorafenib, Cabozantinib and Lenvatinib were obtained commercially from Carbosynth Limited (Berkshire, UK). HepG2, Hep3B and Huh7 cell lines were obtained from American Type Culture Collection (ATCC; LGC Standards, S.L.U., Barcelona, Spain). HCC cell lines were maintained in supplemented Minimum Essential Medium with Earle's Balanced Salts (MEM/EBSS) at 37°C in a humidified incubator with 5 % CO<sub>2</sub>. Cells were seeded at a density of 100,000 cells/cm<sup>2</sup> in 2D culture. Different parameters related to cell death and proliferation were associated with the expression of proapoptotic (Bak, Bax, tBid and Bim) antiapoptotic (Bcl-2, Mcl-1 and Bcl-xL) and regulatory (Beclin-1) Bcl-2 family members assessed by Western-blot analysis.

#### Results:

The administration of tyrosine kinase inhibitors induced cell death and reduced cell proliferation. This effect was associated with an upregulation of tBid and Bim expression in liver cancer cells. This effect was not observed in Hep3B and Huh7 which were less responsiveness to the proapoptotic and antiproliferative properties of tyrosine kinase inhibitors.

#### Conclusions:

The induction of cell death and antiproliferative properties of tyrosine kinase inhibitors were associated with the increase of the expression of different proapoptotic Bcl-2 family members. This expression appeared to be regulated by p53.

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