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

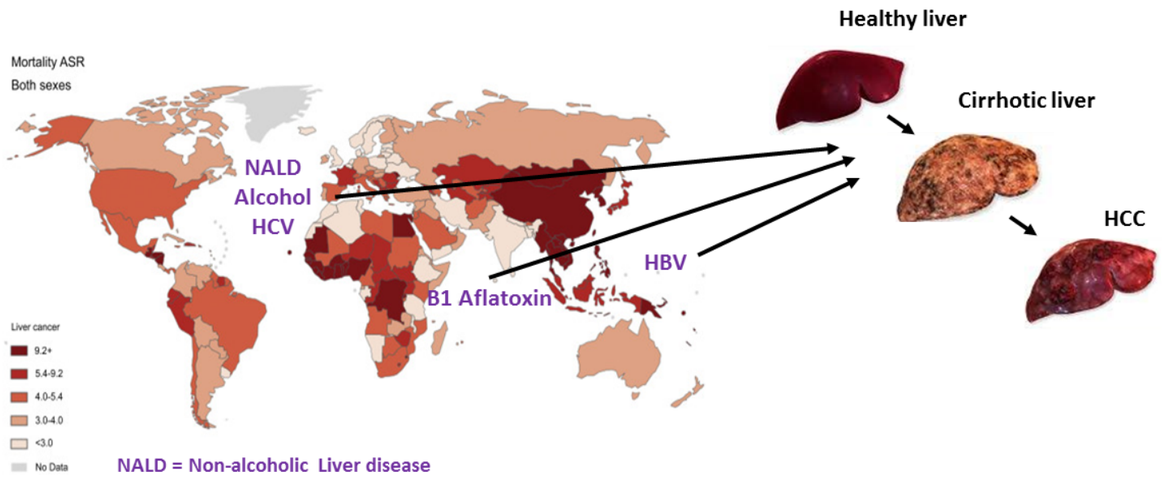
María Isabel Caballos Gómez (1); Jordi Muntané Relat (1)

(1) Institute of Biomedicine of Seville (IBiS), Hospital University "Virgen del Rocío"/CSIC/University of Seville, Seville, Spain

Hepatocellular carcinoma

One of the 10 most frequent neoplasias (6th most frequent)
HCC= Most frequent liver cancer (>80% cases)
749000 new cases/year

Different ethiologies according to the geographic incidence:

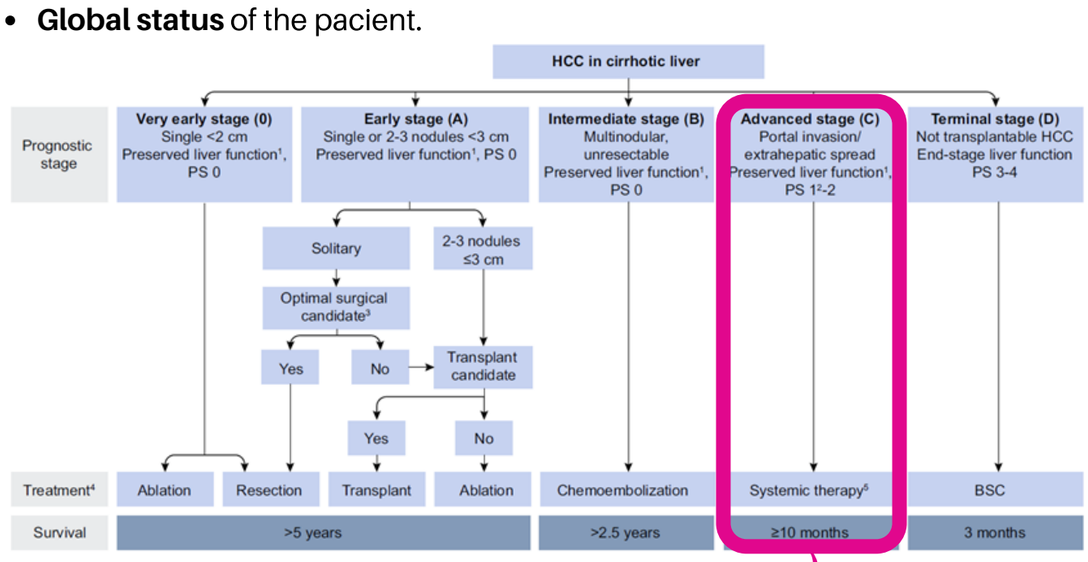


Arabsalmani, M., Mirzaei, M., Soroush, A., Towhidi, F., & Salehiniya, H. (2016). Incidence and Mortality of Liver Cancer and their Relationship with the Human Development Index in the World. Biomedical Research and Therapy, 3(09), 800-807.

HCC Disease Stages

Divided according to:

- **Number, size** & **vascular invasion** of the tumour.
- Presence of **extrahepatic tumours**.
- Hepatic **function**.
- **Global status** of the pacient.



Systemic therapy = **Tirosine kinase (TK) inhibitors**

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018 Volume 69, Issue 1, Pages 182–236

TK-inhibitors effect on liver cancer cells

1. Inhibits tumor **growth** and **vascularisation** inhibiting grow factor receptors.
2. Enhances cell death by **TRAIL** ((TNF)-related apoptosis-inducing ligand) by reducing the effect of **tyrosine phosphatases**.
3. Enhances cell death by **apoptosis**

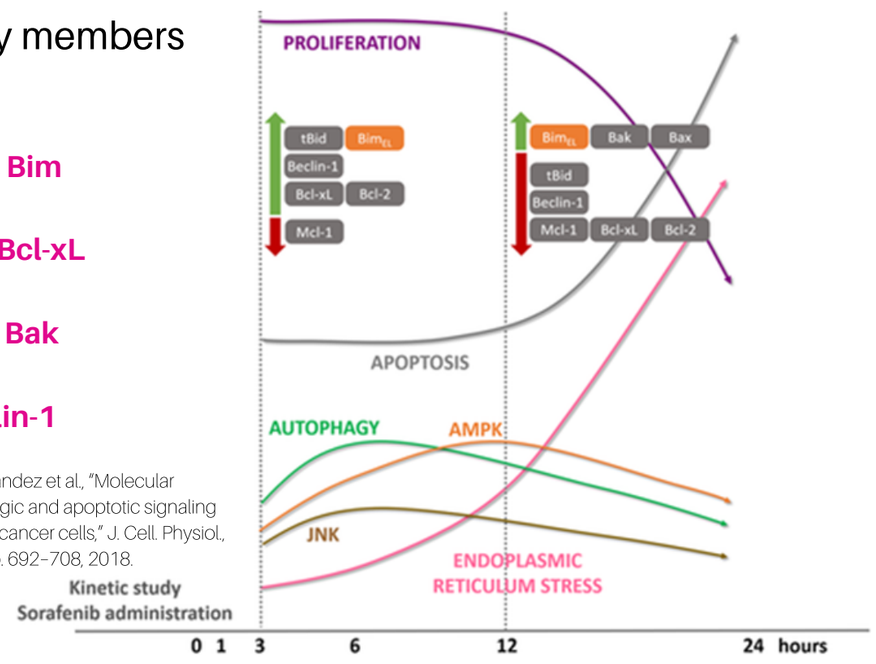
Induced by ER stress (IRE-1 and eIF2-α dependent) → **Autophagy** (1) → **Apoptosis** (2)

Autophagy-apoptosis shift

Bcl-2 family members

- Proapoptotics: **tBid, Bim**
- Antiapoptotics: **Bcl.2, Bcl-xL**
- Effectors: **Bax, Bak**
- Regulator: **Beclin-1**

M. A. Rodríguez-Hernández et al., "Molecular characterization of autophagic and apoptotic signaling induced by sorafenib in liver cancer cells," J. Cell. Physiol., vol. 234, no. 1, pp. 692–708, 2018.



Objectives

Molecular characterization of autophagic and apoptotic signaling induced by tyrosine kinase receptors inhibitors in 3 different cancer cell lines.

To assess the effect of p53 in the apoptotic pathway.

Cell lines

HepG2 -- WT p53 expression
Hep3B -- Nonsense p53 mutation
Huh7 -- p53 mutated isoform

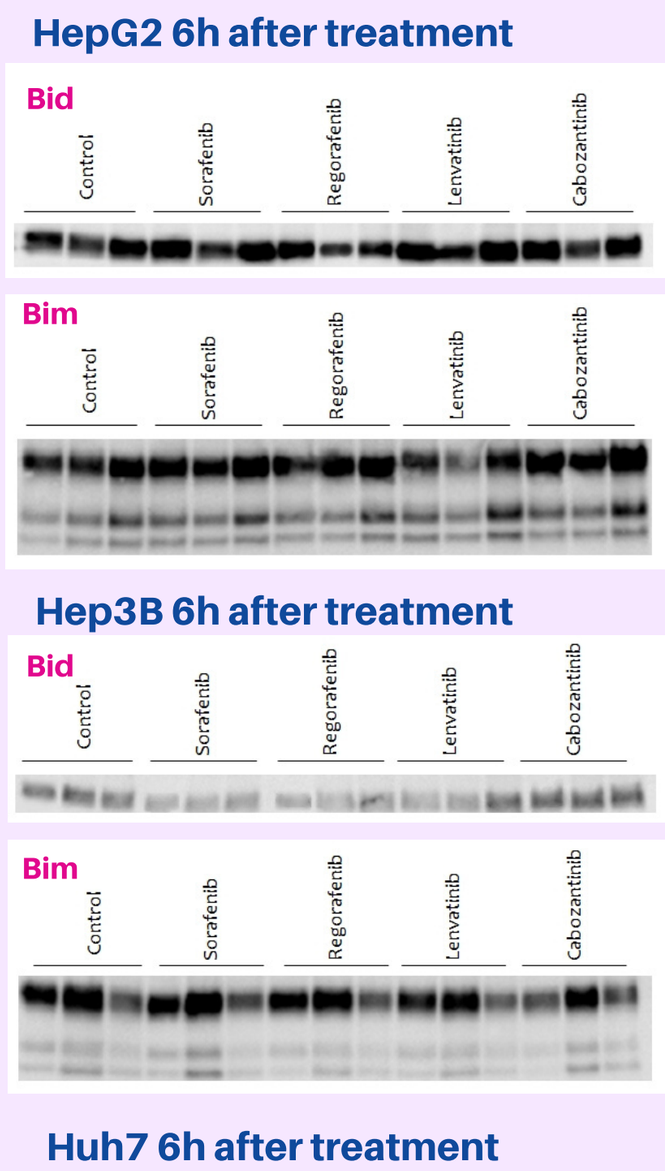
Drugs

Sorafenib -- 1st line treatment
Regorafenib -- 2nd line treatment
Lenvatinib | Clinical studies
Cabozantinib

Results

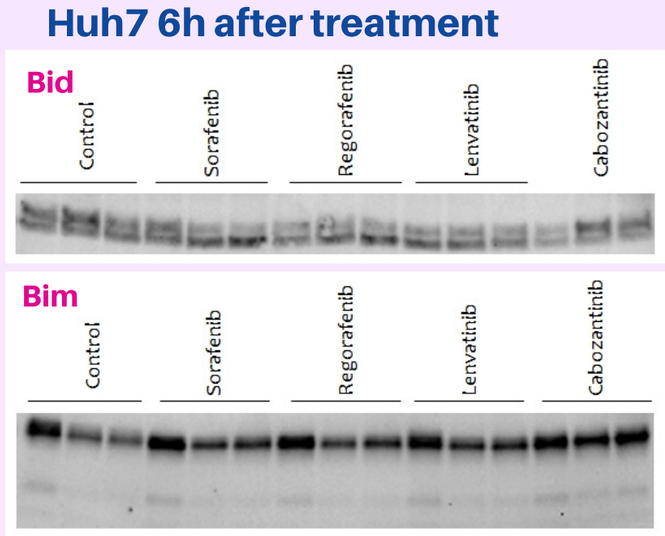
The administration of tyrosine kinase inhibitors induced cell death and reduced cell proliferation. This effect was associated with an upregulation of tBid and Bim expression in liver cancer cells (HepG2). This effect was not observed in Hep3B and Huh7 which were less responsiveness to the proapoptotic and antiproliferative properties of tyrosine kinase inhibitors.

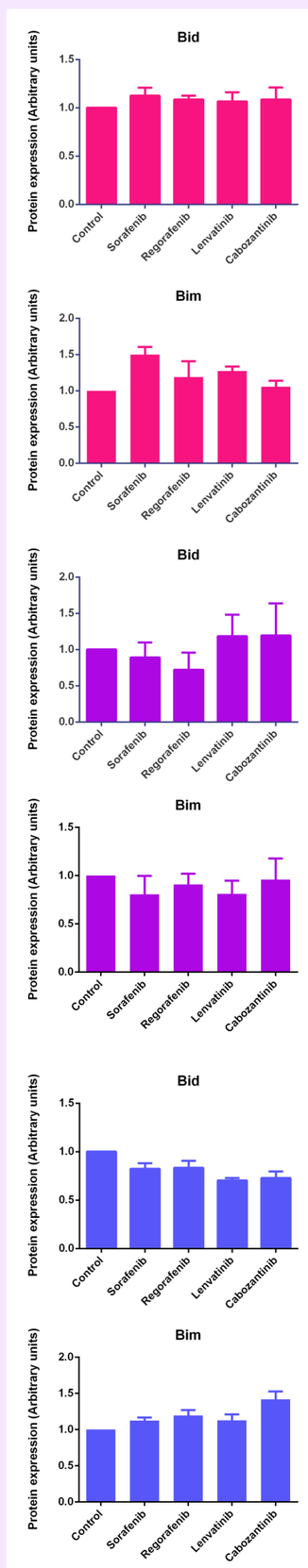
HepG2 6h after treatment



Hep3B 6h after treatment

Huh7 6h after treatment





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.