View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Revistas UPO (Universidad Pablo de Olivade)

Talk

Effect of cell dedifferentiation and genetic p53 profile in the expression of Bcl-2 family members in tyrosine kinase inhibitor-treated liver cancer cells

Raúl Fernández Rodríguez, Matilde Revuelta Gonzalez (1) y Jordi Muntané (2)

(1) Department of Physical, Chemical and Natural Systems, University Pablo de Olavide,Crta. De Utrera Km 1, 41013 Sevilla, Spain.

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

Tutor académico: Matilde Revuelta González

Keywords: Hepatocellular carcinoma; Sorafenib; Regorafenib; Lenvatinib; Cabozantinib; Bcl-2 family; Apoptosis

ABSTRACT

Motivation: Hepatocellular carcinoma (HCC) is the fifth most common type of liver cancer and the second most frequent cause of cancer-related death worldwide [1]. The recommended first-line treatment for patients with locally advanced disease and well-preserved liver function is Sorafenib with a mean overall survival of 11 months [2]. Other drugs have been developed to increase the therapeutic arsenal of treatments such as Lenvatinib [3], Regorafenib [4] and Cabozantinib [5]. The Bcl-2 protein family plays a central part in the control of apoptosis [6]. Bcl-2, Bcl-XL and Mcl-1 are antiapoptotic members Bax, Bak, Bid, and Bim are proapoptotic members. The cytoprotective function of Bcl-2 proteins stems from their ability to antagonize Bax and Bak, and thus prevent apoptosis. [7]. The aim of the present study was the comparative analysis of the tyrosine kinase inhibitors in cell death and proliferation, and the expression of Bcl-2 family members according to the differentiation degrees and p53 genetic profile in liver cancer cells.

Methods: Sorafenib, Regorafenib, Cabozantinib, and Lenvatinib were obtained commercially from Carbosynth Limited. Parameters were assessed in differentiated cells: HepG2 (ATCC/LGC Standards, SLU, Barcelona, Spain) and Huh7 (Apath LLC, Brooklyn, USA), and dedifferentiated cells: JHH2 and JHH4 cell lines obtained from the Japanese Collection of Research Bioresources Cell Bank (Tokyo, Japan). Cells were negative for mycoplasma contamination. HCC cell lines were maintained in supplemented Minimum Essential Medium with Earle's Balanced Salts at 37°C in a humidified incubator with 5 % CO2. Cells were seeded at a density of 10^5 cells/cm2 in 2D culture. Different parameters related to cell death and proliferation were associated with the expression of 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 differentiated liver cancer cells (HepG2 and Huh7) compared to dedifferentiated cells (JHH2 and JHH4, respectively). In addition, the lack of p53 in liver cancer cells (Huh7 and JHH4) had a lower degree in the expression compared to their p53 wild type counterpart (HepG2 and JHH).

Conclusions: The dedifferentiation of cancer cells and mutated p53 reduce the upregulaupregulation of Bim and Bid induced by Sorafenib and Regorafenib in liver cancer cells.

REFERENCES

[1] P. R. Galle et al., "EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma," J. Hepatol., 2018.
[2] J. M. Llovet et al., "Hepatocellular carcinoma," Nat. Rev. Dis. Prim., 2016.
[3] M. Kudo et al., "Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial," Lancet, 2018.
[4] J. Bruix et al., "Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial," Lancet, 2017.
[5] G. K. Abou-Alfa et al., "Cabozantinib in patients with advanced and progressing hepatocellular carcinoma," N. Engl. J. Med., 2018.
[6] S. McGurk, "The Molecular Biology of Cancer: A Bridge from Bench to Bedside – Second edition" Nurs. Stand., 2013.
[7] A. Shamas-Din, J. Kale, B. Leber, and D. W. Andrews, "Mechanisms of action of Bcl-2 family proteins," Cold Spring Harb. Perspect. Biol., 2013.