Berberine - Supportive Action Cancer

Subjects: Oncology
Contributor: Anna Och

Berberine is very promising as the anticancer agent. Berberine not only possesses documented proapoptotic activity, which is in the focus of attention, but also seems to be a very important and promising compound in combined cancer treatment. Sensitization and elimination of drug resistance are very promising trends in the berberine research. What is more, berberine exhibits low toxicity towards healthy cells, which makes it safe for clinical use and proves its activity in biochemical disorders.

Keywords: berberine ; sensitization ; drug resistance

1. Introduction

The promising applications of berberine are limited by the poor pharmacokinetics of the compound. Nevertheless, berberine seems to be very effective and possible to use in combined treatment with other chemotherapeutics or therapies. In terms of sensitization, berberine can be considered as a photosensitizing agent in photodynamic therapy. In a study on renal cancer with human renal tubular epithelial cells derived from the normal kidney HK-2 cell line and human cell lines ACHN and the 786-O cell line, berberine increased the level of autophagy and the level of reactive oxygen species. Berberine induced apoptosis in these cells by induction of caspase 3. Low expression of genes of human telomerase reverse transcriptase and vascular endothelial growth factor-D was observed after combined exposure. Furthermore, polo-like kinase 3 exhibited overexpression after treatment with berberine combined with photodynamic therapy [1]. It has also been described that berberine is a promising potential sensitizer for the radiotherapy of hepatocellular carcinoma, where Nrf2, i.e., a master transcription factor in oxidative damage, is required for this effect of berberine [2][3].

2. Supportive Action of Berberine—Sensitization and Drug Resistance

Sensitization of breast cancer cells to chemotherapeutics seems to be the most promising approach as regards the sensitizing activity of berberine, but other cells, e.g., hepatocellular carcinoma, leukemic, ovarian and lung cancer cells were also described. In the breast cancer MDA-MB-231 cell line, berberine sensitized cancer cells to methyl methanesulfonate, cisplatin and camptothecin. Simultaneously, no synergistic effects with hydroxurea and olaparib were observed. The mechanism of sensitization is probably based on interference of berberine with DNA repair protein—XRCC1 (X-ray repair cross-complementing protein 1)—mediated base excision. As suggested by Gao et al., this may be a basic mechanism in the use of berberine in the therapy of breast cancer [4].

Combination therapy of berberine and cisplatin markedly enhanced the death of other ovarian cancer cells by inducing necroptosis and apoptosis in the ovarian cancer OVCAR3 cell line and primary ovarian cancer cells with a dose- and time-dependent effect. The apoptosis was caspase-dependent, while the necroptosis accompanied the activation of the RIPK3-MLKL pathway [5]. In combination with gefitinib in non-small-cell lung cancer, berberine inhibits epithelial–mesenchymal transition [6].

The combined treatment with doxorubicine showed in vitro and in vivo reduction of repopulation in hepatocellular carcinoma treatment, achieving a synergic effect inhibiting the Caspase-3-iPLA2-COX-2 pathway [7] and a better therapeutic p53-independent effect than doxorubicin alone in leukemic cells [8]. Berberine was found to reverse doxorubicin resistance in MCF-7 and (ADR)-resistant MCF-7 breast cancer cells by inhibiting autophagy, which makes it a promising agent for clinical application in breast cancer treatment. As a suppressor of autophagy, berberine inhibits formation of autophagosome in MCF-7/ADR cells by blocking the accumulation of protein LC3II associated with autophagy. This results in reversal of doxorubicin resistance and reduced cell proliferation. Cellular accumulation of p62 and inhibition of autophagy were also observed. Berberine acted by modulating the PTEN/Akt/mTOR signaling pathway [9].

The supportive activity of berberine in combined treatment is not clarified and needs further research. Importantly, the formulation seems to play a key role. Doxorubicin conjugated to poly (lactic-co-glycolic acid) and used for encapsulation of berberine induced cell cycle arrest in the sub-G1 phase, significant depolarization of the mitochondrial membrane and necrosis in the breast cancer MDA-MB-231 cell line. In vivo studies revealed a very high increase in the half-life and in the plasma drug concentration in such a mode of distribution [10]. Additionally, a nanocarrier hyaluronic acid-conjugated Janus formulation codelivering doxorubicin and berberine exhibited enhanced tumor accumulation and biocompatibility [7]. Maiti et al. described that berberine in combination with curcumin as solid lipid curcumin particles had higher bioavailability and showed higher anticancer effects in cultured cancer cells than in the natural state. In comparison of single and combined treatment of solid lipid curcumin particles and berberine in the human neuroblastoma SH-SY5Y cell line and the human glioblastoma U-87MG and U-251MG cell line, a higher rate of glioblastoma cell death, enhanced fragmentation of DNA, substantially decreased levels of ATP and reduced potential of mitochondrial membrane were observed in the cotreatment of solid lipid curcumin particles and berberine [11].

Novel formulations seem to be crucial in the sensitizing efficacy described above and are important in increasing berberine efficacy itself. For example, the novel berberine complex targeting telomerase appeared to induce dysfunction of mitochondria, damage of the DNA telomere and cell-cycle arrest [12]. Berberine preloaded into folic acid, targeting Janus gold mesoporous silica nanocarriers, exerted a highly potent antitumor effect in patients with liver cancer and ensured good biosafety and effective protection of normal tissues [13]. It is worth mentioning that berberine is a compound with proven ability to bind to G-quadruplexes. Currently, berberine has also been proven to increase the affinity of iminopyrenyl-β-cyclodextrin for the DNA duplex, which may be important in terms of developing new therapeutic formulations [14].

References

1. Lopes, T.Z.; de Moraes, F.R.; Tedesco, A.C.; Arni, R.K.; Rahal, P.; Calmon, M.F. Berberine associated photodynamic therapy promotes autophagy and apoptosis via ROS generation in renal carcinoma cells. Biomed. Pharmacother. Biomed. Pharmacother. 2020, 123, 109794.
2. You, X.; Cao, X.; Lin, Y. Berberine enhances the radiosensitivity of hepatoma cells by Nrf2 pathway. Front. Biosci. Landmark Ed. 2019, 24, 1190–1202.
3. Ashrafizadeh, M.; Fekri, H.S.; Ahmadi, Z.; Farkhondeh, T.; Samarghandian, S. Therapeutic and biological activities of berberine: The involvement of Nrf2 signaling pathway. J. Cell. Biochem. 2020, 121, 1575–1585.
4. Gao, X.; Wang, J.; Li, M.; Wang, J.; Lv, J.; Zhang, L.; Sun, C.; Ji, J.; Yang, W.; Zhao, Z.; et al. Berberine attenuates XRCC1-mediated base excision repair and sensitizes breast cancer cells to the chemotherapeutic drugs. J. Cell. Mol. Med. 2019, 23, 6797–6804.
5. Liu, L.; Fan, J.; Ai, G.; Liu, J.; Luo, N.; Li, C.; Cheng, Z. Berberine in combination with cisplatin induces necroptosis and apoptosis in ovarian cancer cells. Biol. Res. 2019, 52.
6. Zheng, F.; Li, J.; Ma, C.; Tang, X.; Tang, Q.; Wu, J.; Chai, X.; Xie, J.; Yang, X.-B.; Hann, S.S. Novel regulation of miR-34a-5p and HOTAIR by the combination of berberine and gefitinib leading to inhibition of EMT in human lung cancer. J. Cell. Mol. Med. 2020, 24, 5578–5592.
7. Zhang, F.; Jia, Y.; Zheng, X.; Shao, D.; Zhao, Y.; Wang, Z.; Dawulieti, J.; Liu, W.; Sun, M.; Sun, W.; et al. Janus nanocarrier-based co-delivery of doxorubicin and berberine weakens chemotherapy-exacerbated hepatocellular carcinoma recurrence. Acta Biomater. 2019, 100, 352–364.
8. Liu, J.; Zhu, Z.; Liu, Y.; Wei, L.; Li, B.; Mao, F.; Zhang, J.; Wang, Y.; Liu, Y. MDM2 inhibition-mediated autophagy contributes to the pro-apoptotic effect of berberine in p53-null leukemic cells. Life Sci. 2020, 242, 117228.
9. Wang, Y.; Liu, Y.; Du, X.; Ma, H.; Yao, J. Berberine Reverses Doxorubicin Resistance by Inhibiting Autophagy Through the PTEN/Akt/mTOR Signaling Pathway in Breast Cancer. OncoTargets Ther. 2020, 13, 1909–1919.
10. Khan, I.; Joshi, G.; Nakhate, K.T.; Kumar, R.; Gupta, U. Nano-Co-Delivery of Berberine and Anticancer Drug Using PLGA Nanoparticles: Exploration of Better Anticancer Activity and In Vivo Kinetics. Pharm. Res. 2019, 36, 149.
11. Maiti, P.; Plemmons, A.; Dunbar, G.L. Combination treatment of berberine and solid lipid curcumin particles increased cell death and inhibited PI3K/Akt/mTOR pathway of human cultured glioblastoma cells more effectively than did individual treatments. PLoS ONE 2019, 14, e0225660.
12. Qin, Q.-P.; Wang, Z.-F.; Huang, X.-L.; Tan, M.-X.; Luo, Z.-H.; Wang, S.-L.; Zou, B.-Q.; Liang, H. Two telomerase-targeting Pt(II) complexes of jatrorrhizine and berberine derivatives induce apoptosis in human bladder tumor cells. Dalton Trans. 2019, 48, 15247–15254.

13. Li, X.-D.; Wang, Z.; Wang, X.-R.; Shao, D.; Zhang, X.; Li, L.; Ge, M.-F.; Chang, Z.-M.; Dong, W.-F. Berberine-loaded Janus gold mesoporous silica nanocarriers for chemo/radio/photothermal therapy of liver cancer and radiation-induced injury inhibition. Int. J. Nanomed. 2019, 14, 3967–3982.
14. Suganthi, S.; Sivaraj, R.; Enoch, I.V.M.V. Molecular encapsulation of berberine by a modified β-cyclodextrin and binding of host: Guest complex to G-quadruplex DNA. Nucleosides Nucleotides Nucleic Acids 2019, 38, 858–873.