Effects of topoisomerase inhibitors that induce DNA damage response on glucose metabolism and PI3K/Akt/mTOR signaling in multiple myeloma cells.

Abstract:
Hallmarks of cancer cells comprise altered glucose metabolism (aerobic glycolysis) and differences in DNA damage response (DDR). Glucose transporters (GLUT), glycolytic enzymes such as hexokinase (HK) and metabolic pathways (e.g. PI3K/Akt/mTor) have been shown to be upregulated in multiple myeloma and other cancer cell lines. Here we have investigated the effects of clinically used inhibitors of topoisomerase, of DDR and of the PI3K/Akt/mTor pathway on glucose metabolism and on cell survival in multiple myeloma cells. The effects of DNA damaging topoisomerase inhibitors (doxorubicin, etoposide, topotecan), non-DNA damaging agents (bortezomib, vincristine) as well as of molecular inhibitors of DNA damage related kinases PIKKs (KU55933 [ATM], NU7026 [DNA-PKcs]) and PI3K/Akt/mTor signaling (BEZ235 [PI3K/mTor], MK-2206 [Akt]) were analyzed 24 hours after treatment of OPM-2 multiple myeloma cells. For this purpose we monitored [18F]-FDG uptake, cell viability using an ATP assay and expression of GLUT-1, hexokinase II (HKII), cleaved caspase-3 and cleaved PARP via Western-blotting. All topoisomerase inhibitors used could upregulate expression of GLUT-1 and HKII in OPM-2 cells, resulting in elevated
[18F]-FDG uptake and promotion of cell survival. In contrast, bortezomib and vincristine induced a decline in [18F]-FDG uptake combined with early induction of apoptosis. Combination treatment with topoisomerase inhibitors and molecular inhibitors of PIKK and PI3K could reverse elevated [18F]-FDG uptake, as observed after application of topoisomerase inhibitors only, and aggravate induction of apoptosis. Thus, elevated glucose consumption in OPM-2 cells can be reversed by targeting both DDR and PI3K/Akt/mTOR signaling, thus providing a promising strategy in the treatment of cancer.

Zeitschriftentitel / Abkürzung:  
Am J Cancer Res

Jahr:  
2015

Band:  
5

Heft / Issue:  
5

Seiten:  
1649-64

Sprache:  
eng

Pubmed:  

TUM Einrichtung:  
Nuklearmedizinische Klinik und Poliklinik; Frauenklinik und Poliklinik; Hals-, Nasen-, Ohrenklinik und Poliklinik

Occurences:  
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Hals-Nasen-Ohrenklinik und Poliklinik > 2015
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Frauenklinik und Poliklinik > 2015
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Nuklearmedizinische Klinik und Poliklinik > 2015

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