ABSTRACT

Melanoma is a complex malignant disease characterized by increasing incidence and mortality. Melanoma biology is complicated and comprises many aberrant genes and signaling pathways. Treatment of melanoma relies on surgery, the role of radiation therapy and chemotherapy are limited. In advanced disseminating and metastasizing melanoma chemotherapy largely fails and that is why new approaches are being sought including identification of deregulated molecules or processes which could be used as targets. Some of these targets center on frequently aberrant cell death regulating mechanisms. Some traditional cytostatic drugs such as inhibitors of topoisomerases although useful in other types tumors so far proved useless in treatment of melanoma. Nevertheless, expression of topoisomerases in melanoma is often high, thereby enabling at least theoretically their use as targets for chemotherapeutical intervention.

Aim of this study was to assess the cytoxicity and proapoptotic effect of campthotecin (topoisomerase I inhibitor), etoposide (topoisomerase IIα inhibitor) and their combination in selected human melanoma cell lines.

We found that campthotecin may induce apoptosis by a combination of mechanisms including p53 as well as p73 and kaspase-2. Etoposide-induced cell death in Bowes melanoma cells included DNA damage pathway, kaspase-2 but also its direct effect on mitochondria. Combination of campthotecin and etoposide proved to have superior cytotoxic and proapoptotic potential irrespective of tp53 gene status. Also, in wild-type tp53 Bowes cells, apoptosis proceeds via p53-dependent pathway while in mutant-type tp53 SK-Mel-28 cells an important role is being played by stress activated kinases; i.e. p38 and JNK.

Thus the results suggest that topoisomerase I and IIα inhibitors induce versatile stress signaling in melanoma cells which may lead to apoptosis. Individual cell lines feature subtle differences in their response and thus detailed testing of these differences may constitute useful platform for our better understanding of melanoma biology.