A Novel Nanoformulated Hybrid Molecule as a Promising Strategy for the Treatment of Melanoma

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Aims

Melanoma is recognized as the most aggressive and deadly form of skin cancer, with increasing incidence, high multidrug resistance and low survival rates. This work aimed to demonstrate the anti-melanoma potential of a new compound by evaluating its potential cytotoxicity (*in vitro*) and the therapeutic effect in murine models either in its free or in PEG liposomal forms.

Methods

The new compound, a hybrid molecule (HM), combining a triazene nucleus and melanocytotoxic phenols, was assessed for its cytotoxicity on several cancer cell lines and normal keratinocytes by the MTT assay. A Guava assay, a cell cycle distribution analysis and the evaluation of tyrosinase activity were also performed in melanoma cells.[1] Liposomal formulations of HM were prepared by the dehydration-rehydration method, followed by extrusion.[2] The antitumor activity of HM formulations was evaluated in xenograft and metastatic murine melanoma models, where B16F10 cells were injected by sc and iv routes in C57Bl/6 mice, respectively. Caspase and tyrosinase activities were also assessed.[3]

Results

HM displayed considerable toxicity in melanoma, colon, breast and pancreas cancer cell lines (38 μM ≤ IC50 ≤ 64 μM), which was higher than temozolamide (TMZ, IC50 > 75 μM), an available commercial drug. Moreover, a higher percentage of dead and apoptotic cells was observed for HM compared to TMZ, which may be related with a G0/G1 cell cycle arrest as evidenced by flow cytometric analysis. A reduction in tyrosinase activity was also observed. HM was efficiently incorporated (~100%) in long circulating liposomes, highly homogenous, with a mean size of 100 nm. In the xenograft melanoma model, HM nanoformulations demonstrated a remarkable reduction on the tumor progression, compared to free HM, particularly at a dose of 12 mg/kg. Moreover, a strong correlation between tumor growth inhibition, increased caspase activity and decreased tyrosinase activity in tumor protein extracts was observed for mice receiving HM nanoliposomes. In addition, HM nanoliposomes led to a marked reduction of lung metastases compared to non-treated control mice, as macroscopically observed, and confirmed by histopathological analysis.

Conclusions

HM was efficiently incorporated in an inexpensive and efficacious nanosized lipid formulation that showed a notable antitumor activity. Therefore, the results establish liposomal HM as a highly promising therapeutic approach for melanoma treatment.

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References

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