Abstract: P11

Induction of PCD in tamoxifen-resistant oestrogen receptor positive (ER +) advanced breast cancer after combined therapy with ER antisense oligonucleotides and vinorelbine-tartrate encapsulated in DRV liposomes

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1. Introduction

Anti-oestrogen drugs such as tamoxifen have become the treatment of choice for hormone sensitive breast cancer. Nevertheless, despite the antagonistic effect in breast cancer, tamoxifen results in an enhanced incidence of endometrial carcinogenesis in treated women. Furthermore, tamoxifen resistance develops due to alterations in oestrogen receptors (ER), which are then unable to bind oestradiol and DNA.

2. Objective

To circumvent this chemoresistance, we used ER antisense oligonucleotides for ER downregulation combined with the cytostatic action of vinorelbine tartrate in DRV liposomes.

3. Methods, materials and results

We obtained tamoxifen-resistant breast carcinoma tissue by fine needle biopsy from a patient. Tumour cells were isolated by the collagenase method. Immunocytochemical (ICC) and PCR analysis demonstrated upregulation of the ER and the *bcl-2* oncogene. Antisense oligodeoxynucleotides and vinorelbine-tartrate were encapsulated in DRV liposomes. Transmission electron microscopy showed receptor-mediated endocytosis of liposomal oligonucleotides and vinorelbine-tartrate molecules into cellular secondary lysosomes, where liposomal bilayers disintegrated releasing vinorelbine and oligonucleotides intracellularly. Vinorelbine molecules depolymerised cytoplasmic microtubules blocking tumour cells at G2/M stage of the cell cycle. According to ICC and PCR analysis, ER antisense oligonucleotides complexed to the mRNA through the complimentary DNA downregulating ER. Furthermore, bcl-2 was downregulated due to vinorelbine. 72 h post incubation, we observed irreversible apoptotic signs of the D2 stage, the formation of apoptotic bodies, which are phagocytosed by adjacent tumour cells, implying a bystander killing effect. Furthermore, clonogenicity, metabolic activity (MTT), DNA synthesis (BrdU) and trypan blue viability tests of treated tumour cells exhibited greater cytotoxicity compared with untreated control tumour cells.

4. Conclusion

The inactivation of the ER gene combined with the anti-bcl2 and cytostatic action of vinorelbine, induced irreversible D2 apoptotic signs with a subsequent bystander killing of advanced chemoresistant breast tumour cells.

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