Abstract Form

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Cancer-targeted gene therapy for delivering endostatin-cytosine deaminase fusion protein with 5-fluorocytosine suppresses ovarian tumor growth

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Background

There are currently no effective therapies for advanced ovarian cancers, which are associated with angiogenesis dependent peritoneal dissemination. Target gene therapy is an attractive strategy due to the benefit of tumor-specific expression of therapeutic genes. Here, we investigated its therapeutic effect in anti-angiogenesis for advanced ovarian cancer treatment.

Methods

To ensure cancer-specific targeting and efficient delivery for advanced ovarian cancer treatment, we developed an ovarian cancer-specific construct (Survivin-VISA-EndoCD) composed of the ovarian cancer specific promoter survivin in a transgene amplification vector (VISA) to express an endostatin-cytosine deaminase fusion protein (EndoCD), which contains an endostatin domain that has retained its tumor targeting ability for anti-angiogenesis and a cytosine deaminase domain that converts the prodrug 5-fluorocytosine into the chemotherapeutic drug 5-fluorouracil.

Results

Survivin-VISA-EndoCD was found to be highly specific, to selectively express EndoCD in ovarian cancer cells, and to induce cancer cell killing *in vitro* and *in vivo* without affecting normal cells. Survivin-VISA-EndoCD had a strong synergistic effect in combination with cisplatin treatment in ovarian cancer cell lines. Intra-peritoneal treatment with DNA-liposome complexes controlled tumor growth and significantly prolonged survival times in mice bearing advanced ovarian cancers. Importantly, there was virtually safer when EndoCD was expressed with Survivin-VISA than with CMV.

Conclusions

Cancer targeted gene therapy to express EndoCD plus 5FC had significant anti-cancer and specific tumor target effects without suffering systemic toxic in normal tissue for ovarian cancer treatment. Thus, current study provides a promising strategy worthy of development in clinical trials treating advanced ovarian cancer via cancer-targeted gene therapy.

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