

## Micelle-encapsulated thiostrepton is an effective nanomedicine for inhibiting tumor growth

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The oncogenic transcription factor FoxM1 is an attractive therapeutic target in the fight against cancer, because it is over expressed in a majority of human tumors. We identified thiazole antibiotic thiostrepton as inhibitor of FoxM1 and as proteasome inhibitor. We explored the potential *in vivo* anticancer properties of thiostrepton, delivered through nanoparticle encapsulation to xenograft models of breast and liver cancer. We encapsulated thiostrepton into micelles assembled from amphiphilic lipid-PEG (polyethylene glycol) molecules, where thiostrepton is solubilized within the inner lipid compartment of the micelle. Upon assembly, hydrophobic thiostrepton molecules are solubilized into the lipid component of the micelle shell, formed through the self assembly of amphiphilic lipid-PEG molecules. Maximum accumulation of micelle thiostrepton nanoparticles (100 nm in diameter, -16 mV in zeta-potential) into tumors was found at 4 hours post-administration and was retained for at least 24 hours. Upon continuous treatment, we found that nanoparticle-encapsulated thiostrepton reduced tumor growth rates of MDA-MB-231 and HepG2 cancer xenografts. Furthermore, we show for the first time the *in vivo* suppression of the oncogenic FOXM1 after treatment with thiostrepton. Immunoblotting and immunohistochemical staining also showed increased apoptosis in the treated tumors, as indicated by cleaved caspase-3 expression. Our data suggest that the thiazole antibiotic/proteasome inhibitor thiostrepton, when formulated into nanoparticles, may be highly suited as a nanomedicine for treating human cancer. Furthermore, we found that combination of thiostrepton in nanoparticles and bortezomib reduced tumor growth rates more efficiently than compared with when administered alone in xenograft and DEN-PB models of human cancer. Increased induction of apoptotic activity in tumors was found to be associated with the growth inhibitory activity of combination treatment. Further examination additionally revealed that combination-treated tumors exhibited reduced proteasome activity, compared with non-treated and single drug-treated tumors. These data suggest that this drug combination may be useful as a therapy for solid tumor

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## Acute utero-cervical angle: A challenge in high dose rate (HDR) brachytherapy for cervical cancer patients

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**Purpose:** Cervical cancer patients having acute utero-cervical angle is a challenge in HDR brachytherapy. The hard uterine tandem cannot be introduced through this acute angle into the uterine canal to reach the fundus. Incidence of uterine perforation or suboptimal application is high in this situation. Our aim is to describe a new technique facilitating insertion of uterine tandem through acute utero-cervical angle.

**Patients and Methods:** MRI pelvis was done to evaluate the patient before brachytherapy. The uterine length was measured from the MRI sagittal image. Under general anesthesia, the cervix was dilated without introducing the sound or dilators into the uterine cavity to prevent uterine perforation. The distal part of a large size (16 or more) Foley catheter was cut (length equal to the distal thinner part of the uterine tandem) and a marker (one silk suture) was put on it denoting the uterine length. The foley-catheter-cut was introduced through the dilated cervical canal and it can pass the acute utero-cervical angle smoothly into the uterine cavity to reach the fundus. The uterine tandem was introduced to the uterus through the foley-catheter-cut without risk of uterine perforation. Two appropriate ovoids were inserted and the whole system was fixed as usual. CT-scan pelvis was done to evaluate the application and start dosimetry planning.

**Results:** This new method was used successfully for 3 patients.

**Conclusion:** We introduced a new simple method facilitating uterine tandem insertion in a uterus with acute utero-cervical angle decreasing the risk of uterine perforation and suboptimal application.

**Keywords:** Brachytherapy, Cervical cancer, Utero-cervical angle.

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