GOTHENBURG EXPERIENCE WITH AT-211-MX35 FOR TARGETING OVARIAN CARCINOMAS

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This review will cover the efforts in Gothenburg to evaluate the potential of ^{211}At radioimmunotherapy (RIT) in the treatment of small tumor deposits of ovarian cancer in the abdominal cavity.

The lifetime risk of ovarian cancer is 1% – 2% in European and American women. Despite seemingly successful surgery followed by chemotherapy, most patients will relapse, most frequently in the abdominal cavity, and succumb to the disease. Despite newer systemic chemotherapy regimens, the outcome has not improved over the past decade. RIT with various β-emitters has displayed promising results, though an international Phase III study of ^{90}Y-labeled antibody showed no improvement in time to relapse or survival. This disappointing result might be explained by the long range of β-emitters, which results in poor irradiation of tumors less than a few millimeters in size. In treating small tumors, the short range and high LET of α-emitters such as ^{211}At offer a significant advantage by more effectively irradiating targeted small cell clusters.

The PET & Cyclotron Unit at Rigshospitalet in Copenhagen has regularly since ~10 years delivered ^{211}At to the research group in Gothenburg led by Prof. Ragnar Hultborn and Prof. Lars Jacobsson. Astatine-211 is isolated from the irradiated target by dry distillation. The ^{211}At-labelling method gives stable radiochemical yields of 70% – 80% with the antibody conjugate's tumor-cell binding ability essentially preserved. The activity of an antibody batch of 0.1 – 0.5 mg is approximately 300 – 500 MBq, sufficient for extensive animal experiments or for treatment of one patient.

The therapeutic effect has been studied in a series of experiments in vitro and in nude mice with intraperitoneal (i.p.) growth of microscopic ovarian cancer tumors. A number of parameters related to the injected antibody conjugate and stage of tumor growth have been investigated. Studies of toxic effects for bone-marrow, kidneys, and the peritoneal membrane indicate that microscopic tumors smaller than approximately 0.1 mm are likely sterilized without any serious organ toxicity. Tumor cure probability decreases with increasing tumor size.

Dosimetry, based on biokinetic modeling and a Monte Carlo program, indicates that an absorbed dose of approximately 20 Gy is needed for tumor eradication in nude mice. The tolerance level (mean absorbed dose) is estimated to be ~0.5 Gy for bone-marrow and ~10 Gy for kidneys. For the peritoneal membrane preliminary results indicate a tolerance level of more than ~25 Gy. Comparisons with low-LET 60Co irradiation for tumor-growth inhibition and bone-marrow toxicity both resulted in an RBE of ~5.

Based on the promising results of the animal studies, a clinical Phase I study of 9 patients was started in 2005 (and published in 2009). Thirty to 120 MBq of 211At-MX35 F(ab′)2 was administered i.p. in 1.1 – 2.2 L of fluid (Extraneal). Dosimetric calculations were mainly based on the ^{21}1At activity in samples of peritoneal fluid, blood, and urine 0 – 48 h post

injection. Gamma camera imaging did not reveal uptake in any major organs except the thyroid. The thyroid uptake was reduced by potassium perchlorate or potassium iodide in the last four patients. No adverse effects of the treatment were observed subjectively or in the laboratory parameters. In conclusion, therapeutic absorbed doses of ^{211}At in microscopic tumors in the abdominal cavity of humans are achievable without significant toxicity.