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Preclinical = evaluation of a=20 radiopharmaceutical for refractory prostate tumor = radionuclide=20 therapy.

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Objective

Bombesin (BBN) is an analog of human gastrin = releasing=20 peptide (GRP). BBN receptors =F1 in particular the GRP = receptor=20 =F1 have been shown to be massively overexpressed in = several=20 human tumor cells, especially of prostate cancer (PC), = and=20 could be an alternative as target for their diagnosis = and/or=20 treatment by nuclear medicine techniques. A large = number of=20 BBN analogs had already been investigated for this = purpose and=20 have shown to reduce tumor growth in mice. = Nevertheless, most=20 of the studied analogs exhibited high abdominal = accumulation,=20 especially in pancreas and intestine, in preclinical = studies.=20 This abdominal accumulation may represent a problem in = clinical use of radiolabeled BBN analogs probably due = to=20 serious side effects to patients. In this work we = describe the=20 preclinical and toxicological evaluation of a new = bombesin=20 derivative planned at IPEN/CNEN-SP =F1=20 177Lu-DOTA-Phe-Gly5-BBN(6-14) =F1, in order to develop = a new=20 radiopharmaceutical for prostate tumor treatment.

Methods

The peptide was radiolabeled with lutetium-177 and = both=20 TLC-SG and HPLC were applied to evaluate the = radiochemical=20 purity of the preparations. Biodistribution, = pharmacokinetics,=20 whole body and scintigraphic studies were performed in = both=20 healthy Balb-c and xenografted Nude mice, in order to=20 characterize the biological properties of = radiopeptide. Acute=20 intravenous toxicity was evaluated by the cold peptide = in rats=20 (adults, male, 250 g) tail vein. The total mass = injected was=20 10 times higher the mass that would be administrated = to humans=20 per kg, considering an adult of 70 kg. Rats=ED = behavior was=20 evaluated for two hours post injection and water and = food=20 intake as well as body weight were assessed daily. In=20 addition, after 24 hours and 7 days p.i. the animals = were=20 sacrificed in groups of five, the blood was collected = for=20 hematology and serum biochemistry and organs were = dissected=20 for histological evaluation.

Results

The bombesin derivative showed fast blood clearance = (T=BD =3D=20 10 minutes), rapid renal excretion, low abdominal=20 accumulation, short effective half-life and =

significative and=20 specifically target to human prostate tumor (PC-3) = cells in=20 mice. Neither mortality nor changes in animals=ED = behavior were=20 observed during all times analyzed in toxicological = studies.=20 Food and water intake, body weight, hematological and=20 biochemical parameters did not show differences of=20 toxicological and/or statistical relevance between the = experimental and control groups. In addition, = macroscopic=20 examination of organs did not demonstrate any changes = and=20 there were no histological findings of toxicological=20 significance.

Conclusions

These results suggested that the bombesin = derivative=20 studied is a promising radiopharmaceutical for = prostate tumor=20 treatment and also that it can be considered = potentially safe=20 for human use in clinical studies. Further studies are = in=20 development in order to produce a GMP grade = radiopeptide for=20 applying in Phase I clinical studies.=20