An open, single dose, anti-tumor effect study of 2-hydroxyflutamide as a controlled release product (Liproca® Depot) injected into the prostate in patients with localized prostate cancer

842

Häggman, M.H.[1], Ladjevardi, M.S.[1], Ahlström, H.A.[2], Lennernäs, B.[3], Tolf, A.T.[4], Weis, J.W.[2], Wassberg, C.W.[2], Axén, N.[5], Bjartell A.[5] Lennernäs H.[6], Tammela, T.L.[7]

[1]Uppsala University Hospital, Dept. of Urology, Sweden, [2]Uppsala University Hospital, Dept. of Radiology, Sweden, [3]Gothenburg University, Dept of Oncology, [4]Uppsala University Hospital, Dept. of Pathology, Sweden, [5]LIDDS AB, Virdings allé 32b, Uppsala, Sweden, [6]Uppsala University, Dept. of Pharmaceutics, Sweden, [7]Tampere University Hospital, Dept. of Urology, Finland

Objectives: To evaluate tolerability and antitumor effect of Liproca® Depot, a novel controlled release formulation with 2-hydroxyflutamide (2-HOF), after a single dose injection into the prostate for patients with localized prostate cancer (PC) scheduled for radical prostatectomy (1).

Material & Methods: 23 patients (46-72 years) with PC stage ≤T2c, Gleason ≤3+4, PSA <15 ng/ml and prostate volume (PV) <80 ml were included from two university hospitals in Sweden and Finland. The Liproca® Depot formulation (200 mg/ml 2-HOF) was injected with TRUS guidance mainly into the peripheral zone. In part 1 (P1) the target dose was 15 vol-% of the PV (6 weeks follow-up).
In part 2 (P2), the target dose was 30 vol-% (8 weeks follow-up). Effect was evaluated by histopathology (HE), magnetic resonance imaging (MRI), proton (1H) single-voxel spectroscopy (MRS) and spectroscopic imaging (MRSI), and PSA and PV at 6/8 weeks. In P2 urinary flow, residual urine, I-PSS were added.

Results: The injected dose, and the resulting effect on plasma values, PSA and PV are shown in Table 1. HE showed partial anti-androgen effect in 12/18 patients in P1 and in 2/5 patients in P2.

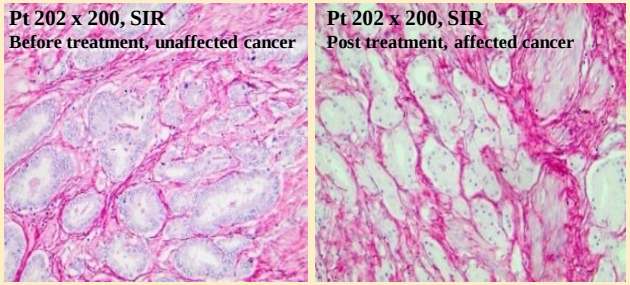

Fig. 1. Representative tissue sections from a patient before and after treatment indicating a partially increased cytoplasm/nucleus ratio as well as cyto-plasmic clearance and stroma reduction/cell clustering in treated tissues.

Global MRI morphology changes were found in 9/19 evaluable patients while changes in tumor tissue were seen in 12/22 patients.

A global reduction in detectable metabolites were seen in many patients using MRSI.

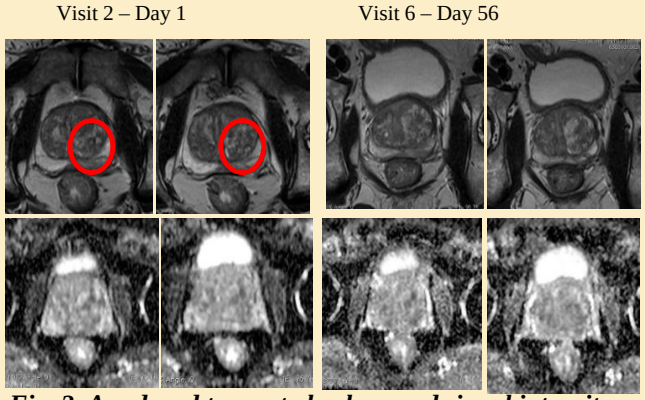

Fig. 2. A reduced tumor to background signal intensity close to the lesion (injection site).

Intraprostatic injections of Liproca® Depot 6-8 weeks prior to RP caused an overall reduction in prostate tissue metabolism along with morphological changes interpreted as cellular atrophy. The plasma concentrations of 2-HOF were significantly lower than after oral flutamide treatment and consequently the testosterone levels were unaffected. A dose-response relationship for the reduction of PSA and PV where observed for P1 to P2.
Side effects were acceptable, the most common being hematuria, dysuria, urinary retention, impaired voiding and urinary tract infection. Only transient effects on urine flow, residual volume and I-PSS were recorded.

Table 1. Dose, plasma PK, and changes in main effect parameters; mean (range).

Marker	Part 1 (n=18)	Part 2 (n=5)
Dose, mg	920 (600-1300)	1740 (1140-2400)
Dose, vol-%	14 (8-21)	27 (16-32)
Testosterone change, %	-1.8 (0.5-2.3)	9.3 (4.9-15.6)
C_{max} 2-HOF, ng/ml	77 (19-182)	152 (68-218)
PSA reduction, %	16 (0-57)	23 (15-39)
PV reduction, %	10 (0-37)	12 (7-18)

Conclusions: This novel intraprostatic injectable drug was well tolerated and PSA and PV values were reduced. The study indicates that the injected dose can be increased beyond 30 vol-% with expected increased anti-tumor effect.

1. Sjögren E, Tammela T.L, Lennernäs B, Taari K, Isotalo T, Malmsten L.Å, Axén N, Lennernäs H, Molecular Pharmaceutics, 2014; 11:3097-111.