

Intravesical EOquin (E09) in the Treatment of Superficial Bladder Cancer

JA Witjes, AG van der Heijden

Dept Urology, UMCN St Radboud, Nijmegen, the Netherlands

Gino Lenaz M.D., Shanta Chawla M.D.

Spectrum Pharmaceuticals, Inc. Irvine, CA 92618

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Abstract

EOquin and mitomycin-C (frequently used as intravesical agent in superficial bladder cancer) are structurally similar but the mechanism of action differs with regard to the ability of oxygen to reverse the activation process and elevated levels of reductases in tumor tissue.

Why intravesical application of EOquin?:

The bladder is a **hypoxic region**; there is a **presence of DT-diaphorase enzyme** in the bladder; there is **no systemic uptake**.

In an in vitro experiment we used 4 bladder cancer cell lines that were treated for 60 min. with 0-200 µg/mL MMC or EOquin at 37°C or 43°C. Cell survival was determined by an MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazoliumbromide) assay. All cell lines were human bladder cancer cell lines, 253J and RT4 are p53 wild type, RT112 has a p53 mutation in exon 7 and T24 has a p53 mutation in exon 5. LD₅₀ data showed that with 43°C versus 37°C, 31.3% less MMC was needed and 42.5% less EOquin was needed. Moreover EOquin is on average 26 times (6-78) more potent than MMC. Differences in p53 status did not influence the outcome of the cell viability. This in vitro study showed that the low LD₅₀ combined with the significant synergy makes EOquin a promising agent for intravesical use.

Phase 1:

We initiated a phase I escalating dose study for intravesical Eoquin (R. Puri, Bradford Royal Infirmary, UK) 6 patients were treated with weekly instillations of 0.5-16.0 mg/ 40 mL of EOquin. In fixed dose study 4 additional patients were treated with 6 weekly instillations with 4.0 mg/40 mL of Eoquin. Because of local side effects (reversible chemical cystitis) the dose was set to 4mg, which all patients tolerated.

Safety: EOquin instillations are safe, No systemic toxicity

Efficacy: Escalating Doses: 5 out of 6 patients showed complete response; 4 are free of disease at 12-24 months follow up
Fixed Dose: 4 out of 4 patients showed complete response, which is persisting at 6-9 months follow up.

Phase 2:

Currently a phase II marker lesion study is being conducted in the UK and the Netherlands in 7 centers. 44 patients will be enrolled, and treated intravesically with a dose of 4 mg/40mL of EOquin for 6 consecutive weeks. The primary study objectives are to determine the overall marker lesion response. Secondary objectives are time to recurrence, duration of response and overall safety. The marker lesion concept has been tested in several EORTC studies and is valid and safe.

Patients with 2 to 10 Ta-T1, G1 or G2 tumors are selected and all tumors are resected except one marker lesion of 0.5-1.0 cm before the start of treatments with EOquin. The marker lesions are biopsied or resected 2-4 weeks after the last instillation as control. UP to September 10, a total of 30 patients have been enrolled, out of which 19 patients are evaluable for response. Preliminary results show that there are 11 complete responders and 8 non or partial responders with the follow up of six months there is no relapse. Side effects were mild and reversible, usually dysuria and hematuria. One patient had a SAE (chemical cystitis).

Conclusion:

The preliminary results of these marker lesion studies indicate substantial activity of intravesical EOquin with no systemic toxicity. The side effect profile is comparable with those of other intravesically applied chemotherapeutic agents.