INFECTION

Which antibiotics for UTI?

A multinational, open-label, analyst-blinded, randomized clinical trial has shown that 5-day nitrofurantoin is more likely to result in clinical and microbiological resolution of acute, uncomplicated lower urinary tract infection (UTI) than single-dose fosfomycin. These results could influence future treatment decisions for managing UTI.

This study included 513 women aged >19 years who were not pregnant and had at least one symptom of acute lower UTI (including dysuria, urgency, frequency, and/or suprapubic tenderness), a positive urine dipstick test, and no known colonization or previous infection with antibiotic-resistant uropathogens. Participants were randomly assigned 1:1 to receive 100 mg nitrofurantoin orally three times a day for 5 days or 3 g fosfomycin orally as a single dose. Clinical evaluation and urine culture collection was undertaken at 14 and 28 days after therapy completion.

The primary outcome was clinical response, which could be clinical resolution of infection at day 28 (defined as complete resolution of signs and symptoms of UTI without failure), failure (defined as a requirement for a change of antibiotics or discontinuation owing to lack of efficacy), or indeterminate (no objective evidence of infection but persistent symptoms). Secondary outcomes included bacteriological response and adverse events.

Overall, 93% of women completed the trial and 73% had a confirmed positive baseline culture. Clinical resolution at day 28 was achieved in 70% of patients receiving nitrofurantoin and 58% receiving fosfomycin ($P=0.004$) and the effect was greater in the subgroup of patients with confirmed *Escherichia coli* infections (78% versus 50% of patients, $P<0.001$). At the earlier time point of day 14, a significant difference was also observed (75% versus 66% achieving complete response, $P=0.03$). Microbiological resolution was attained in 74% of participants in the nitrofurantoin group and 63% in the fosfomycin group ($P=0.04$); again the difference was more pronounced in the subset of patients with confirmed *E. coli* infections (72% versus 58%, $P=0.03$). The median duration of symptoms was one day longer in women receiving nitrofurantoin than those who had fosfomycin, but this difference was not statistically significant. Adverse events were relatively infrequent and occurred at similar rates in both treatment groups.

These data show that 5-day treatment with nitrofurantoin results in better clinical and microbiological outcomes 28 days after completion of therapy than single-dose fosfomycin in women with acute, uncomplicated lower UTI. Treatment of women presenting with acute UTI could be influenced by these findings.

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ORIGINAL ARTICLE Huttner, A. et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. *JAMA* 319, 1781–1789 (2018)

PROSTATE CANCER

Surfaceome profiling for NEPC target antigens

Prostate adenocarcinoma and neuroendocrine prostate cancer (NEPC) have distinct surfaceomes, which can be used to discriminate between the subtypes and might provide target antigens for immunotherapy.

The advent of CAR T cell therapy shows the potential of targeting treatment to cell-surface markers. However, identifying target antigens in prostate tumours — NEPC in particular — is problematic, as markers upregulated in adenocarcinoma are often downregulated in neuroendocrine disease.

Lee and colleagues derived a panel of putative human cell surface proteins, which was able to differentiate adenocarcinoma and NEPC. Differential expression analysis showed that the expression of 330 cell surface genes was enriched fourfold or more in adenocarcinoma, whereas expression of 438 cell surface genes

was enriched in NEPC. Comparison of the genes to identify molecular functions showed that those enriched in NEPC were related to neural function, including synaptic signalling, nervous system development, and neurotransmitter transport, whereas those of adenocarcinoma were involved in secretion, immune response, and inflammatory response, enabling differentiation of the subtypes.

RNA sequencing (RNA-seq) gene expression analysis of human prostate cancer cell lines showed heterogeneous expression of androgen-regulated genes, neuroendocrine markers, and epithelial markers across the two tumour types, and corresponded with expression of previously established markers. These differences were used to nominate potential tumour antigens for prostate adenocarcinoma and

PROSTATE CANCER

Aptamer effective in vivo

A new study demonstrates that an aptamer conjugated to the chemotherapeutic monomethyl auristatin F (MMAF) specifically targets prostate cancer cells, inhibits tumour growth, and improves survival in mice.

Aptamers are oligonucleotides or peptides that bind to a specific target molecule and can be used to deliver cytotoxic agents, similar to antibody–drug conjugates; however, aptamers can have higher specificity and are easier to produce and modify than antibodies. “Previous work mostly focused on conjugating aptamers to traditional chemotherapeutics, such as doxorubicin, but trials with antibody–drug conjugates have shown that tumour targeting drugs are only effective when coupled to agents that are too toxic to administer alone,” explains Bethany Powell Gray, first author of the paper. “Thus, we sought to develop and test a new class of targeted anticancer therapeutics:

aptamers conjugated to highly toxic chemotherapeutics.”

The team selected the aptamer using a cell-internalization SELEX approach. Two independent selections that included several prostate cancer cell lines identified the RNA aptamer E3, which specifically internalizes into malignant but not benign prostate cells. In vitro characterization showed that E3 targets cells derived from different prostate cancer subtypes and with varying androgen sensitivity. The researchers then tested the toxicity of E3 conjugated to the tubulin polymerization inhibitor MMAF or the related MMAE, of which only MMAE is membrane permeable. MMAE–E3 was considerably more toxic to prostate cancer cells than MMAF–E3, but a nontargeted MMAE control conjugate was also toxic, in contrast to the MMAF version; hence, MMAF–E3 was used in further studies. As MMAF is highly toxic, the team also developed a DNA-based antidote to E3, which inhibited 90% of E3