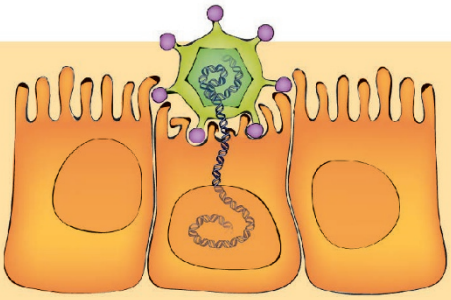
Nature Reviews Urology | Published online 12 Sep 2017; doi:10.1038/nrurol.2017.150

BLADDER CANCER

IFNα-2b gene transfer: a new approach for BCG-resistant disease



Macmillan Publishers Limited

Patients with BCG-resistant or recurrent high-grade non-muscle-invasive bladder cancer (NMIBC) have a high risk of disease progression; however, many are unable or unwilling to undergo radical cystectomy, therefore, alternative, less-invasive treatment approaches are required. Now, data from a phase II trial involving 43 patients with refractory or relapsed NMIBC reveal the clinical potential of IFNα-2b gene transfer, delivered using a recombinant adenovirus.

Following promising initial results with intravesical infusions of recombinant, pegylated IFNα-2b, researchers generated a replication-deficient adenovirus vector (rAd–IFNα-2b) designed to transfect the urothelium with the human IFNα-2b gene, in order to obtain longer-lasting effects. Syn 3, a polyamide surfactant, was included in the vector, having previously been shown to dramatically enhance the efficiency of gene transfer during preclinical investigations.

Patients received a single infusion of either low-dose (1×10^{11} viral particles (vp)/ml) or high-dose (3×10^{11} vp/ml) rAd–IFNα-2b, followed by retreatment at 4, 7 and 10 months after the initial treatment. Efficient delivery of IFNα-2b DNA was confirmed by significant increases in urinary IFNα-2b levels in all patients on days 2, 4 and 12 after the initial infusion. A total of 14 patients (35% of the cohort) remained disease free at a follow-up duration of 12 months, with similar recurrence-free survival (RFS) of 33.3% and 36.8% in the high-dose and low-dose groups, respectively. This trial used a phase II design, with no placebo or standard-of-care comparison group; however, the outcomes of patients receiving rAd–IFNα-2b in this study are superior to those of patients receiving valrubicin, the only FDA-approved agent for patients with BCG-refractory bladder cancer, which typically provides 1-year RFS of around 10%.

The majority of patients receiving rAd–IFNα-2b had durable responses (>24 months), with two patients having disease recurrence, at 21 and 28 months, respectively. An additional patient with an upper-tract tumour died after 17 months of follow-up monitoring. Virtually all patients (85%) had at least one treatment-related adverse event, although all were grade ≤3 in severity, including urinary urgency or dysuria (both in 40% of patients), and fatigue in 32.5% of patients. No patients discontinued treatment owing to adverse events.

These findings demonstrate the safety and tolerability of rAd–IFNα-2b, with promising levels of effectiveness. The results of an ongoing phase III trial of this approach, involving a much larger cohort of patients, are eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLE Shore, N. D. *et al.* Intravesical rAd-IFNα/Syn3 for patients with high-grade, Bacillus Calmette-Guerin-refractory or relapsed non-muscle-invasive bladder cancer: a phase II randomized study. *J. Clin. Oncol.* http://dx.doi.org/10.1200/JCO.2017.72.3064 (2017)