

## Interferon - combination therapy with low dose BCG

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External sites from Expert M.A.O'Donnell, U of Iowa-

Bladder Cancer Research Institute

BCG+Interferon Alpha for Superficial Bladder Cancer: Physician's protocol

-Projects in Knowledge: New Prospects in the Treatment of Superficial Bladder Cancer.

More on WebCafé: National Bladder Cancer Research Foundation

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Interferon is a naturally produced chemical released by the body in response to viral infections. It can be produced artificially and used as a form of immunotherapy

Although BCG has better track rate as an intravesical immunotherapy for superficial TCC, recombinant interferon-alpha has been shown to work in BCG failures. Tolerability is very good, while toxicity in the form of mild flu-like symptoms is observed in only very few patients. Pilot studies have shown that intravesical interferon therapy can significantly lower the recurrence rate in superficial TCC of the urinary bladder. While significant response was seen in those who had had prior treatment which had failed, response rates in those who had no prior treatment was nearly doubled (30% vs 67%).<sup>1</sup>

In one UK study, CIS patients treated with effective doses (100 million units compared with 10 million units) achieved a complete response of 47 percent.<sup>2</sup> IFN alpha has an important role in superficial bladder cancer treatment, particularly as second line therapy after BCG or intravesical chemo has failed. <sup>3</sup>

### BCG+Interferon

Animal studies have shown the combination to be more effective than that of either single agent alone, and recent research is suggesting that interferon alpha2b is a potent BCG enhancer. Early data showed that BCG + IFN is well tolerated and effective for patients at high risk for disease recurrence and/or progression, even for those that have failed prior BCG therapy. Furthermore, significant reductions in BCG dose (=less side effects) are possible with this regimen without apparent loss in anti-cancer efficacy.

## Trial Results Promising

Dr. Michael O'Donnell, M.D., F.A.C.S., Chief of Urologic Oncology, University of Iowa Hospital & Clinics (formerly of Harvard Medical School in Boston), has been conducting trials using a low dose-BCG + Interferon protocol for superficial bladder cancer and CIS.

Update July 2006:

Final results from a national multicenter phase II trial of combination bacillus Calmette-Guérin plus interferon  $\alpha$ -2B for reducing recurrence of superficial bladder cancer. Fadi N. Joudi M.D.<sup>a</sup>, Brian J. Smith Ph.D.<sup>b</sup>, Michael A. O'Donnell M.D.<sup>a</sup>, Corresponding Author Contact Information, E-mail The Corresponding Author and National BCG-Interferon Phase 2 Investigator Group <sup>a</sup>Department of Urology, University of Iowa, Iowa City, IA 52242-1089, USA <sup>b</sup>Department of Biostatistics, University of Iowa, Iowa City, IA 52242-1089, USA

Results Of 1,007 valuable patients, 59% and 45% of patients naïve to BCG and those having BCG failure, respectively, remained disease free at 24-month median follow-up. Stage T1, tumor size >5 cm, prior BCG failure more than once, and multifocality were all statistically significant risk factors for recurrence.

Conclusions Although BCG plus IFN- $\alpha$  can be effectively applied to both patients naïve to BCG and those having BCG failure, certain patient and tumor characteristics influence durable response.

Urologic Oncology: Seminars and Original Investigations Volume 24, Issue 4, July-August 2006, Pages 344-348  
Proceedings: Annual Meeting of the Society of Urologic Oncology (May 2005). Part III: Advances in Transitional Cell Carcinoma of the Bladder: Diagnosis and Treatment doi:10.1016/j.urolonc.2005.11.026

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Earlier data (see below) showing the efficacy of combo-immunotherapy are being validated by recent trial results:

Salvage intravesical therapy with interferon- $\alpha$ 2b plus low dose bacillus calmette-guerin is effective in patients with superficial bladder cancer in whom bacillus calmette-guerin alone previously failed. O'Donnell MA, Krohn J, DeWOLF WC. Department of Urology, University of Iowa, Iowa City, Iowa, and Division of Urology, Beth Israel Deaconess Medical Center, Boston, Massachusetts. J Urol. 2001 Oct;166(4):1300-5. PMID: 11547062

The use of interferon- $\alpha$  and BCG together in the therapy does more than simply add the power of each treatment to the other, the study revealed. It was shown that 55 percent of patients treated with the combined immunotherapy were disease-free two-and-a-half years after treatment compared to an expected disease-free rate of less than 20 percent for patients treated with another non-surgical (chemotherapy) method. "The combined treatment is up to 40 times more

effective in stimulating the immune system than the use of either interferon or BCG alone," said O'Donnell.

<http://www.uihealthcare.com/news/news/2001/10/08bladdercancer.html>

Excerpt from the abstract:

Patients in whom 2 or more previous BCG courses had failed fared as well as those with 1 failure. Of the 18 failures, 14 occurred at the initial cystoscopy evaluation. Of 22 patients initially counseled to undergo cystectomy 12 (55%) are disease-free with a functioning bladder. Combination therapy was well tolerated.

**CONCLUSIONS:** While longer followup and larger multicenter studies are required to validate these encouraging findings, intravesical low dose BCG plus interferon-alpha2B appears to be effective in many cases of high risk disease previously deemed BCG refractory. However, early failure while on this regimen should be aggressively pursued with more radical treatment options.

For a print-friendly copy of the whole abstract, [click here](#)

A study in the September 2001 issue of UROLOGY has independently confirmed in a group of 15 patients failing multiple course of BCG (6 of whom also failed valrubicin) a 60% complete response/disease free rate (9/15) after 1 (4 patients) or 2 (5 patients) courses of low-dose BCG plus interferon-alpha. Risk of continued intravesical therapy and delayed cystectomy in BCG-refractory superficial bladder cancer: an investigational approach. Luciani LG, Neulander E, Murphy WM, Wajzman Z. Division of Urology, University of Florida, Gainesville, Florida, USA Urology 2001 Sep;58(3):376-9 PMID: 11549484

To learn more, two excellent websites feature details of the protocol, input from other experts in the field:

" New Prospects in the Treatment of Superficial Bladder Cancer. Created by an outstanding faculty of urologists, the cases and corresponding discussions provide practical strategies for approaching the management of superficial bladder cancer, especially among the more challenging clinical scenarios" - <http://www.projectsinknowledge.com/Init/1531U/index.html>

And: Biologic Therapy in Bladder Carcinoma;

BCG+Interferon Alpha for Superficial Bladder Cancer: Physician's protocol

Previous studies:

CO-ADMINISTRATION OF INTERFERON-ALFA 2B WITH LOW DOSE BCG IS EFFECTIVE IN PATIENTS WITH SUPERFICIAL BLADDER CANCER PREVIOUSLY FAILING BCG ALONE. Michael A. O'Donnell, Tracy M. Downs, William C. DeWolf. Boston, MA. (Presented by Michael A. O'Donnell)

**INTRODUCTION AND OBJECTIVES:** Therapeutic alternatives for patients failing prior BCG treatment have shown limited clinical efficacy. Our goal was to determine if combination low-dose BCG with interferon alfa 2B (JFN-Q) would be effective in this difficult clinical situation.

**METHODS:** Thirty eight patients failing one (19) or more than one (19) prior induction course of BCG received 6 weekly treatments of 1/3 dose (27 mg) BCG plus 50 million units (MU) of IFN-a. Additional 3 week mini-series of further reduced BCG (1/10, 1/30, or 1/100th) titrated to symptoms without changing the dose of IFN-a was given for maintenance at 5, 11, and 17 months. In 11 cases, a 2nd induction course with 1/10th BCG plus 100 MU of IFN-a was given. Nearly all patients (37) had multifocal disease; most (33) had failed prior BCG within 6 months; 29 had aggressive disease (stage T1, grade 3, or CIS); 23 had 2 or more prior recurrences; and 12 had disease of over 4 years duration.

**RESULTS:** With mean and median follow-ups of 21 months and a range of 6-39 months, Kaplan-Meier analysis reveals 61% disease free at 12 months and 56% at 24 months. Importantly, patients failing 2 or more prior courses of BCG did just as well as those failing only 1 prior course (58 & 58% vs. 63 & 53% at 12 & 24 months, respectively). Almost all combination therapy failures (14/16) occurred at the first 3- 4 month evaluation permitting successful early radical surgical intervention where appropriate. Only 4/11 benefited from a 2nd induction course. Of 20 patients initially counseled to undergo cystectomy, 12 (60%) are disease free with a functioning bladder as a result of this therapy. Generally, combination therapy with downward BCG titration was well-tolerated and side effects were similar to BCG alone.

**CONCLUSIONS:** Combination intravesical low-dose BCG + IFN-a appears to be an effective alternative for many patients with high risk for disease recurrence and/ or progression previously deemed BCG refractory. However, early failure on this regimen suggests intrinsically resistant disease that should be aggressively pursued with more radical treatment options.

THE JOURNAL OF UROLOGY Supplement April 2000 Vol 163

Dr. O'Donnells findings were confirmed by a study in Singapore:

A PHASE II TRIAL OF BCG COMBINED WITH INTERFERON ALPHA FOR BLADDER CANCER. K. Esuvaranathan, R. Kamaraj, R. S. Moltan, C. Cheng, P. K. Tan, K. P. Toy, S. J. Chia, C. M. Chin. Singapore. (Presented by K. Esuvaranathan)

**INTRODUCTION AND OBJECTIVES:** The aims of this study were to determine whether dose reduction of BCG and the addition of 10MU Interferon alpha- 2b, could lower morbidity and increase efficacy.

**METHODS:** A double-blind randomized controlled study was conducted in patients with aggressive superficial bladder cancer. Morbidity data was carefully collected and the patients underwent 3-monthly surveillance with cystoscopy and urine cytology. All patients received 6+3 instillations of one-third dose BCG with or without interferon alpha or full dose BCG alone.

**RESULTS:** Of 80 patients, there were 20 cases of CIS  $\pm$ 1- papillary tumours; 18 recurrent ra and 36 Ti tumours. The median follow-up was 19 mo (6 -42). Dose reduction of BCG, even with interferon, significantly reduced both local and systemic morbidity ( $p < .01$ ). Overall, the recurrence rates for full-dose BCG, one-third dose BCG and one-third dose BCG plus interferon were 50%, 30% and 10% (Pearson's test,  $p \sim 0.035$ ). All 4 CIS patients responded to combination therapy but 5 of 16 CIS patients treated with BCG alone did not.

**CONCLUSIONS:** These promising results are the best reported for a short course of BCG instillations and warrant the initiation of Phase III trials.

Annual Meeting of the AUA, May, 2000 supplement of the Journal of Urology

See also John Stroop's story.

#### References

1. Alpha-interferon in superficial bladder cancer: a Northern California Oncology Group Study. Torti FM; Shortliffe LD; Williams RD; Pitts WC; Kempson RL; Ross JC; Palmer J; Meyers F; Ferrari M; Hannigan J; et al Stanford University Medical Center, Palo Alto, CA J Clin Oncol 1988 Mar;6(3):476-83 PMID: 3280742 UI: 88171626
2. A randomized controlled study of intravesical alpha-2b-interferon in carcinoma in situ of the bladder. Glashan RW: Department of Urology, Royal Infirmary, Huddersfield, United Kingdom. J Urol 1990;144:658-661. PMID: 2201795 UI: 90355290
3. Superficial bladder cancer: the role of interferon-alpha published erratum appears in J Urol 1998 Oct;160(4):1444] Belldegrun AS; Franklin JR; O'Donnell MA; Gomella LG; Klein E; Neri R; Nseyo UO; Ratliff TL; Williams RD Division of Urologic Oncology, UCLA School of Medicine, Los Angeles, California, USA. J Urol 1998 Jun;159(6):1793-801 PMID: 9598463 UI: 98258410
4. IFN-alpha 2B Enhances Th1 Cytokine Responses in Bladder Cancer Patients Receiving Mycobacterium bovis Bacillus Calmette-Guerin Immunotherapy Authors:LuoY; Chen X; Downs TM; DeWolf WC; O'DonnellMA Harvard Medical School, Boston PMID:0073521 UI: No Cit. ID assigned 3:98-101

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[back to superficial bladder cancer](#)