BCG plus Interferon-alpha for Superficial Bladder Cancer

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Use of Interferon Alfa in Bladder Cancer. Michael A. O'Donnell, MD. Director of Urologic Oncology, University of Iowa Hospitals and Clinics, Iowa City, IA.

Interferon-alfa (IFN-α) is a biological response modifier that has both direct and indirect action against transitional cell carcinoma (TCC), the most common type of bladder cancer. While intravesical IFN-α monotherapy for superficial bladder cancer has limited total effectiveness vis-a-vis chemotherapy or BCG, it can induce long term remissions even in patients that have failed other forms of therapy and does so with a very favorable toxicity profile causing little to no cystitis.

Recently, combining intravesical IFN-α with chemotherapy or BCG is emerging as a new treatment strategy. Preliminary studies of IFN-α plus Mitomycin suggest additive efficacy. Combination therapy of IFN-α with BCG appears especially promising. As a mixed intravesical preparation, these two agents are completely biocompatible. Experimental testing of BCG/IFN-α combination therapy demonstrates a favorable profile on all aspects of the BCG/tumor/immune system interaction. Direct toxic effects of BCG on human bladder cancer lines is enhanced by the addition of IFN-α. The combination also synergistically enhances direct cytokine production by tumor cells, reduces proliferation and upregulates tumor surface markers including histocompatibility antigens and the apoptotic orchestrator Fas. This makes the tumor a better target for immune cell recognition and destruction. Furthermore, IFN-α strongly polarizes the human cellular immune response to BCG in the direction of the favorable T-helper type one (TH1) pathway by down-regulating the antagonistic cytokine IL-10 while upregulating the expression of TNF-α, IL-12, and IFN-gamma. Substantial amplifications in IFN-γ production are achieved against human lymphocytes during in vitro testing, averaging approximately 40-fold while allowing up to a 100-fold reduction in BCG dose. This feature of IFN-α essentially enhances the body's natural immune response to BCG.

Safety and efficacy studies of combination BCG plus IFN therapy in animal models are similarly encouraging. IFN-β, closely related to IFN-α, protects against infection by a related mycobacterial pathogen MAI. BCG plus IFN-α or BCG plus the interferon inducer bropiramine are more effective than either agent alone in the murine MBT-2 and MB-49 bladder cancer models.

Several pilot clinical studies using combination intravesical immunotherapy against superficial bladder cancer have shown promising results. Bercovich (1995) found half dose BCG plus low-dose (10 MU) IFN-α-2B to provide equivalent tumor prophylaxis to full dose BCG but with reduced toxicity. Stricker (1996) reported complete and partial response rates at 12 months for 9/12 and 2/12 patients, respectively, all with aggressive histology. Half dose BCG was given together with IFN-α-2B titrated from 10-100 MU with no serious adverse events. Esuvaranathan (2000) has reported a reduction of recurrence rate from 50% to 30% to 10% at 19 months in a randomized study of 80 patients treated with full-dose BCG vs. 1/3 dose BCG vs. 1/3 dose BCG plus 10 MU IFN-α, respectively. Patient tolerance was also improved in the combination arm. The early results of an open-label combination study by O'Donnell (2000) in 38 high risk patients with superficial TCC that had all previous failed BCG is similarly encouraging. Using 50-100 MU of IFN-α-2B plus BCG in doses ranging from full to 1/100th standard dose, titrated down by prior exposure and tolerance especially during the maintenance phase, complete response rates at 26 months median follow-up is 56% even for patients that have failed BCG monotherapy two or more times before. Toxicity has been no different than with BCG alone. Urinary IFN-γ levels are enhanced or maintained at high levels during therapy.

The use of IFN-α as part of a multidrug cytotoxic chemotherapeutic regimen for advanced urothelial cancers remains provocative. The initial reports of Logothetis et al. showing 30% and 60% PR with IFN-α combined with 5-FU or 5-FU plus platinum, respectively, have not yet been repeated. Parnis (1997) found IFN-α plus cisplatinum to be historically equivalent to cisplatinum alone (35% PR) in a phase II trial involving 22 patients.

Schema for BCG + IFN-α Use

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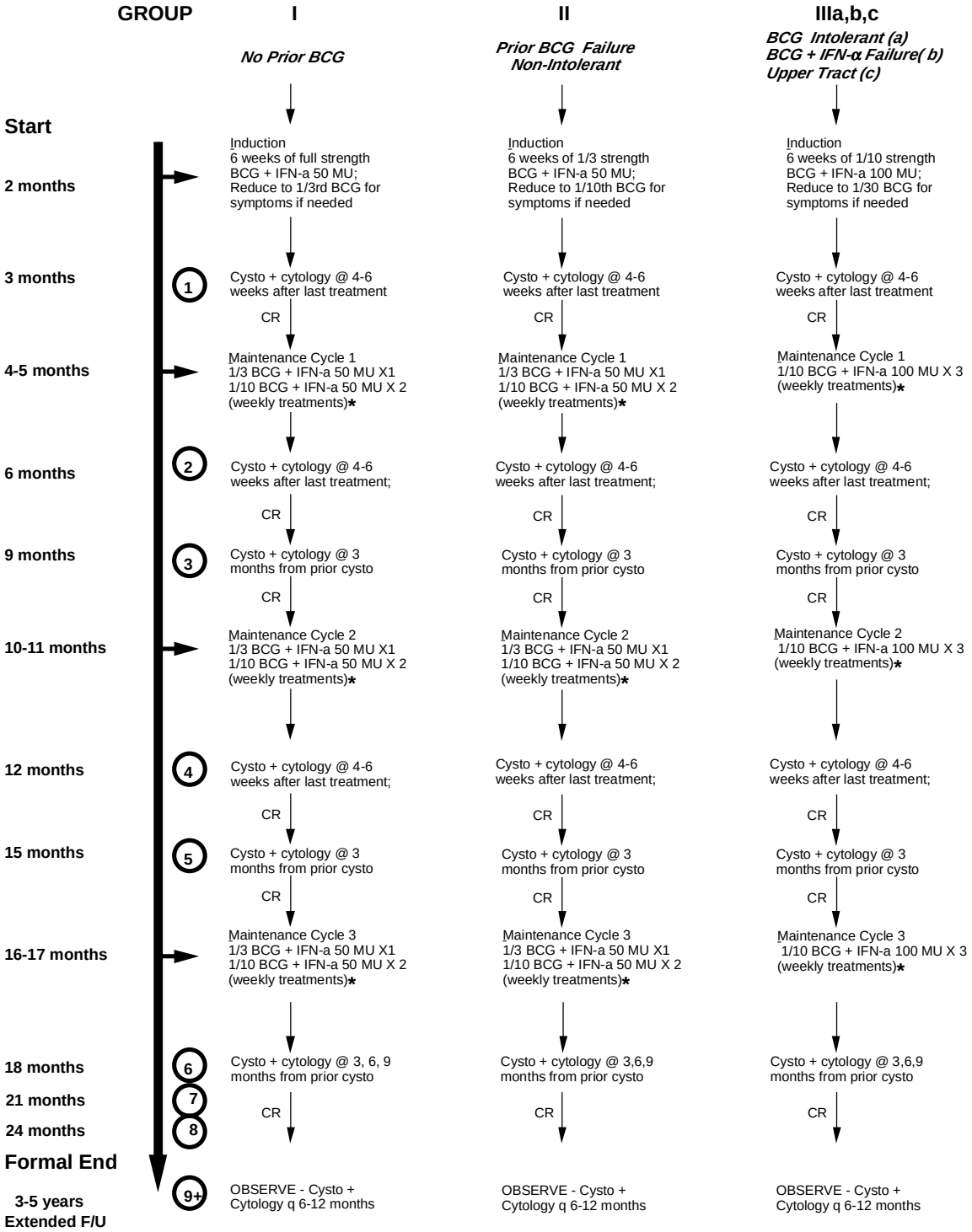
INVESTIGATIONAL



* Further 1/3 BCG dose reductions to 1/30, 1/100 and 1 week delays permitted for severe symptoms

Recommendations for Intravesical Instillation: Patient Preparation

- It is **strongly recommended** that the prior fluids be kept to an absolute minimum and diuretics withheld unless medically necessary.

- **No caffeine** containing beverages 6-8 hours prior to instillation and 2 hours afterward.

- **Do Not** recommend patients force fluids during the first 24 hours post instillation; normal fluid intake is recommended.

- Remind patients to arrive with some fluid in their bladder. This will make it easier to insert the catheter and collect a urine specimen if needed. If you see fresh blood in the urine **the treatment should be postponed.**

- Patients should try to hold medication for a full two hours after instillation but **should not force holding if they feel a strong urgency to void**. Nor should they try to hold medication longer than the recommended two hours.

- Patients may leave the clinic immediately after treatment. Remind them to void the medicine in ~2 hours and to rinse the toilet with 1 cup of bleach thereafter.

Preparation of TheraCys (Connaught) BCG - Interferon-alfa (Intron A) Mixture For Intravesical Instillation

Mixing Components

- Supplied with TheraCys
  - Instillation spike with attached tubing and pinch clamp
  - Phosphate buffered saline (PBS) 50 cc vial
  - BCG diluent - 3 cc vial
  - TheraCys BCG - 81 mg dry weight vial (powder)
  - Vial venting device
- Supplied with Intron A
  - Intron A diluent - 1 cc vial
  - Intron A - 50 Million Unit (MU) vial (powder)
- Provided by site
  - (1) 3 cc and (1) 1 cc Luer-Lok (Tb) syringe with detachable needles
  - Gloves
  - Surgical mask

Reconstitution Directions (perform in this order)

- Intron A reconstitution
  - Set out all materials on flat surface and remove plastic caps off BCG diluent, PBS, TheraCys, Intron A diluent and Intron A powder. Swab rubber tops with alcohol wipe.
  - Withdraw 1 cc of Intron A diluent into the 1 cc Tb syringe and inject into Intron A powder. Swirl gently until solution becomes clear then withdraw entire amount into syringe.
  - Inject entire volume of reconstituted Intron A into 50 cc PBS vial.
  - Repeat prior steps if preparing 100 MU Intron A dose, injecting 2nd 50 MU dose into the same 50 cc PBS vial.
- BCG reconstitution and dose adjustment
  - Attach 3 cc syringe without needle to vial venting device via luer lok.
  - Withdraw BCG diluent into syringe to 3 cc mark.
  - Add 3 cc BCG diluent into amber TheraCys vial. Swirl gently to mix.
  - Withdraw appropriate amount of reconstituted TheraCys into syringe depending on desired BCG dose as follows:
    - Full dose - 3 cc
    - 1/3 dose - 1.0 cc
    - 1/10 dose - 0.3 cc
    - 1/30 dose - 0.1 cc
  - Transfer appropriate amount of BCG directly into 50 cc vial of PBS/Intron A. Discard syringe with vial venting device.

Instillation Directions

- Insert instillation spike with attached tubing and closed pinch clamp into top of PBS vial. Swirl vial to mix completely.
- Invert PBS vial and squeeze priming chamber at base of spike several times until chamber is 1/2 - 3/4 full.
- Remove cover on tubing tip aseptically and release pinch clamp. To ensure good flow down tube squeeze and hold priming chamber to push fluid 1/2 way down tubing. Without releasing the priming chamber reclamp the pinch clamp to vent air in from above. Now release the pinch clamp and check that fluid flows down tube unimpeded. Reclamp pinch clamp to stop flow.
- Aseptically attach tubing tip to patient's catheter, release pinch clamp and allow gravity instillation.

Preparation of TICE (Organon) BCG - Interferon-alfa (Intron A) Mixture For Intravesical Instillation

Mixing Components

- Supplied with TICE BCG
  - Diluent (larger) Mini-Spike pin
  - Active product (smaller) Mini-Spike pin
  - Flexible 9 inch fluid transfer tubing with plastic cap on tip
  - 0.9% Sodium Chloride for injection (NS) 50 ml vial
  - TICE BCG - 50 mg dry weight vial (powder)
- Supplied with Intron A
  - Intron A diluent
  - Intron A - 50 Million Unit (MU) vial (powder)
- Provided by site
  - (2) 1 ml Luer-Lok (Tb) syringes with detachable needles
  - Gloves
  - Surgical mask

Reconstitution Directions (perform in this order)

- Preparatory steps
  - Set out all materials on flat surface, remove plastic caps off NS, TICE BCG vial, Intron A diluent, and Intron A powder. Swab rubber tops with alcohol wipe.
  - Withdraw 1 ml NS (BCG diluent) into Tb syringe through attached needle then remove syringe with attached needle. Cap and set aside for the moment.
- Intron A reconstitution
  - Withdraw 1 ml of Intron A diluent into Tb syringe and inject into Intron A powder. Swirl gently until solution becomes clear then withdraw entire amount into syringe.
  - Inject entire volume of reconstituted Intron A into 50 ml NS vial. Discard syringe.
  - Repeat prior steps if preparing 100 MU Intron A dose, injecting 2nd 50 MU dose into the same 50 ml NS vial.
- BCG reconstitution and dose adjustment
  - Attach larger Mini-Spike to 50 ml NS vial now containing Intron A
  - Attach smaller Mini-Spike to TICE BCG vial.
  - Unscrew needle from previously prepared Tb syringe containing 1 ml of NS (BCG diluent) and attach directly via luer tip to Mini-Spike in TICE BCG vial. Inject full 1 ml into vial, drawing active product into syringe then back into vial 3 times for complete mixing.
  - Withdraw appropriate final amount of reconstituted TICE BCG into the attached syringe depending on desired BCG dose as follows:
    - Full dose - 1 ml
    - 1/3 dose - 0.33 ml
    - 1/10 dose - 0.1 ml
    - 1/30 dose - 0.03 ml
  - Detach syringe containing appropriate amount of BCG and inject directly into 50 ml vial of NS/Intron A mixture. Discard syringe and swirl NS vial to mix.

Instillation Directions

- Attach flexible fluid transfer tubing via luer tip to NS vial containing BCG/Intron A mixture.
- Invert NS vial, remove plastic cap on tip of tubing and squeeze NS bottle to initiate flow.
- Aseptically attach tubing tip to patient's catheter and allow gravity instillation.

Recommendations for Intravesical Instillation: Drug Administration

- Recommended catheter for most men is a 16 Fr latex or silicone coude' foley.

- A 10cc "Urojet" with 2% lidocaine jelly is recommended for men to minimize trauma. Balloon inflation is not generally required.

- Recommended catheter for most women is a 14 Fr straight "robnell-type" with water soluble Sugilube or KY jelly.

- Make an extra effort to completely drain the bladder through the catheter before BCG/IFNα instillation. Apply gentle crede' pressure to facilitate complete emptying.

- In men be sure to pull through the jelly plug by inserting the "urojet" to the catheter and drawing back. This will help to get the residual urine to drain through the catheter.

- Instill the BCG/IFNα within 2 hours of mixing-preferably sooner.

- BCG/IFNα and anything that comes in contact with BCG must be disposed of in a biohazard waste container.

Recommendations for Treatment of BCG Toxicity

Sign/Symptom	Intensity & Description	Therapeutic Response
Cystitis: dysuria, urgency, frequency	0 - None 1 - mild, transient <48 hrs 2 - moderate, < 3 days 3 - mod-severe, > 3 days 4 - severe, persistent >10 days	0,1 - no treatment 2 - antispasmodics 3 - delay &/or reduce dose 4 - cancel further Rx this cycle; add antibiotics +/- steroid taper if persistent
Hematuria (gross)	0 - none 1 - mild, transient <48 hrs 2 - moderate, < 3 days 3 - mod-severe, > 3 days 4 - severe w/ clots or obstruction or >10 days	0,1 - no treatment 2 - push fluids 3 - delay &/or reduce dose 4 - cancel further Rx this cycle
Fever & Chills	0 - None 1 - mild < 100.5, < 48 hrs 2 - moderate < 101.5, < 48hr 3 - mod-severe <102.5,< 48hr 4 - severe >102.5 or > 48 hrs or rigors	0,1 - no treatment or Tylenol 2 - preRx w/ NSAIDs 3 - delay &/or reduce dose; consider fluoroquinolone 4 - cancel all further Rx this cycle, start INH/rifampin
Flu-like Sxs: myalgia, malaise, arthalgias, headache	0 - None 1 - mild 2 - moderate 3 - mod-severe 4 - severe	0,1 - no treatment 2 - NSAIDs 3 - delay &/or reduce dose 4 - cancel further Rx this cycle
Other Adverse Events WHO Criteria	0 - none 1 - mild 2 - moderate 3 - severe 4 - life threatening	0,1 - no treatment 2 - delay &/or reduce dose until condition clears 3 - cancel further Rx this cycle 4 - cancel all future Rx

Antibiotic Guidelines

- Routine use of prophylactic antibiotics is discouraged in the absence of documented bacterial cystitis excepting when the patient has a prosthetic device such as heart value or orthopedic hardware. When antibiotics are indicated, a non-quinolone antibiotic is recommended, preferably a penicillin, cephalosporin, sulfa, or nitrofurantoin.
- Fluoroquinolone antibiotics are cidal to BCG and may be useful for treating early grade 3 toxicity. A minimum of 7 days is probably necessary.
- INH (300 mg/day) plus rifampin (600 mg/day) should be considered for refractory grade 3 or suspected grade 4 toxicity. Vitamin B-6 (50 mg/day) should accompany prolonged treatment. Grade 4 toxicity may require a 3rd drug such as ethambutol (1200 mg/day). BCG is uniformly resistant to cycloserine and this agent should NOT be used. Early systemic steroids (e.g. prednisone 40 mg/day) may be life-saving in cases of frank BCG sepsis. Antibiotics must accompany steroid use.

Severe BCG Cystitis – Recognition, Treatment and Prevention

Most patients receiving intravesical BCG treatment experience mild to moderate irritative bladder symptoms at some point during their therapy (usually lasting 1-3 days). However, a small subset will continue to have moderate to severe symptoms going on for several weeks, even beyond the point where no further BCG is administered. While some respond to conventional antispasmodics (like Ditropan or Detrol) or urinary analgesics (like Pyridium or Urised), many will remain refractory to these agents raising great concern among the patients and health care practitioners.

Before establishing the diagnosis of severe BCG cystitis, it is necessary to rule out other mimicking conditions. The first step should be to check the urinalysis and send off the urine for culture and sensitivity. The UA's for both bacterial UTI's and BCG cystitis show pyuria but the culture for BCG cystitis is typically sterile. While waiting for the culture results, starting a broad-spectrum fluoroquinolone like Cipro, Levaquin or Floxin is appropriate since these antibiotics also have activity against BCG. It is also important to establish with reasonable certainty that the patient does not have recurrent bladder cancer, particularly carcinoma-in-situ or CIS, an aggressive surface spreading form of bladder cancer that can actually cause severe bladder irritation. This is most appropriately diagnosed with a combination of recent cystoscopy with biopsies if appropriate. In addition it is very important to do a urine cytology - a test that looks for shed malignant cells in the urine much like a Pap smear.

Severe BCG cystitis is a condition caused by a hypersensitive response of the body's immune system to either live or dead retained BCG products that become sequestered in the bladder mucosa and submucosa sometimes even within the white blood cells. This is often revealed by diffuse red inflammatory patches in the bladder that microscopically form "granuloma". Most cases of "granulomatous cystitis" are not accompanied by fever. The presence of a relapsing night time fever with drenching night sweats suggests either a very severe form of cystitis or an even more serious condition of systemic BCG infection known as BCG'itis that requires the institution of tuberculosis specific antibiotics such as Isoniazid (INH) and Rifampin and sometimes even hospital admission.

The response of severe BCG cystitis without fever to anti-tuberculosis antibiotics is variable. Isoniazid and rifampin are very slow in action and the addition and/or substitution of the faster acting fluoroquinolones may be advantageous. A minimum trial of 3 weeks of these agents is usually required. Unfortunately, inflammation may persist even after eliminating any residual living BCG. At this point the most likely remedy is the use of an oral Prednisone taper to break the cycle of inflammation. A reasonable dosing schedule for Prednisone is as follows:

Days 1-3: 40 mg 1x/day in am
Days 4-6: 20 mg 1x/day in am
Days 7-9: 10 mg 1x/day in am
Days 10-12: 5 mg 1x/day in am
Days 13-15: 2.5 mg 1X/day in am
Then STOP

If necessary, the taper can be extended or drawn out more slowly over a 3-4 weeks period but most patients begin to respond within a few days and are able to get off the steroids completely within 2-3 weeks. Not all symptoms will completely resolve but improvement should be obvious and allow for more gradual resolution. IT IS VERY IMPORTANT THAT THE ANTI-TUBERCULOSIS ANTIBIOTICS OR FLUOROQUINOLONE BE CONTINUED THROUGHOUT THE PREDNISONE THERAPY AND FOR AT LEAST 2 WEEKS BEYOND BECAUSE THE PREDNISONE CAN WEAKEN THE IMMUNE SYSTEM ALLOWING ANY LIVE BCG TO MULTIPLY. You can probably back off to one agent but you have to keep some BCG-specific antibiotic on board.

In addition, it may be helpful for symptoms to add a new Cox-2 (anti-inflammatory drug) such as Vioxx 25mg/day or Celebrex 200 mg/day during the Prednisone and continuing (if needed) for the next 2-4 weeks. These drugs are generally well tolerated, do not cause stomach upset, and do not thin the blood. They should NOT be given in conjunction with aspirin or other non-steroidal anti-inflammatory agents such as ibuprofen, Motrin, Aleve, etc.

A literature reference substantiating the safe use of Prednisone for this condition is listed below.

Severe Bacillus Calmette-Guerin Cystitis Responds to Systemic Steroids when Antituberculous Drugs and Local Steroids Fail by R Wittes, L Klotz & U Kosecka. J Urology May 1999 pages 1568-69.

Generally the decision to retreat patients with BCG after they have developed severe BCG cystitis must be made with extreme caution. If you must, wait at least 6 months after all inflammation has subsided and restart BCG at a very low dose of 1/30 -1/100th with 100 MU of interferon-alpha. For future reference, one way to avoid this condition is to avoid retreating a patient if the symptoms from the prior weekly treatment have not resolved within 3-5 days or if the UNSPUN urinary WBC count per high powered field (hpf) is greater than 5 (corresponds to ~ 100 WBC/hpf for spun urine). To avoid precipitating this condition, it is acceptable to either delay treatment by 1-2 more weeks and dose reduce (by a factor of at least 3, e.g. 1/3rd to 1/10th) or even omit further treatments in any given cycle depending on the severity of the prior local reaction.

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USE OF COMBINATION BCG PLUS INTERFERON-ALPHA IN THE UPPER URINARY TRACT

The management for upper tract transitional cell carcinoma is problematic because of the technical difficulties involved in diagnosis, follow-up, accurate staging, and delivery of therapeutic agents. The incidence of upper tract TCC is roughly 4% that of bladder cancer but is 3-5 times higher in patients with advanced bladder cancer, those with long duration disease, or patients successfully treated with BCG for aggressive superficial bladder cancer (Stage T1, any grade 3, CIS, or positive cytology). In the setting of a normal contralateral kidney, the standard clinical practice is to perform a radical removal of the entire kidney and ureter (nephroureterectomy). Low-grade localized lesions of the ureter may sometimes be eliminated by segmental resection or local endoscopic ablation, usually with the laser. Intermediate grade lesions may also be treated conservatively when renal function preservation is required but recurrences are common. One particularly difficult problem has been the treatment of a localizing positive urinary cytology to the upper tract for which no visible lesion can be demonstrated. While this most likely represents upper tract CIS, the same high-grade aggressive lesion found in the bladder, there is no consensus for treatment, ranging from observation alone to radical surgery. Topical application of BCG or various chemotherapeutic agents have been tried using adaptations from bladder cancer protocols through indwelling stents or percutaneous nephrostomy tubes. The best successes have been obtained with BCG but concern about systemic infection has severely limited its use. The oral interferon-alpha inducer, bropiramine, resulted in a complete response rate of 48% but did not achieve FDA approval and is no longer available for use in the US.

Combination low-dose BCG plus interferon-alpha has also been applied with success in several patients with upper tract TCC. Fifteen of 18 renal units in 14 patients have had complete responses to therapy with ongoing remissions between 4-32 months. Most had pan-urothelial CIS and most responded in both upper and lower urinary tracts to the therapy segmentally delivered. Combination therapy was administered either in a retrograde fashion via temporary external stents or antegrade via percutaneous nephrostomy tubes. In the former case, a small 4 Fr stent was used to permit flow into the uppermost kidney and drainage around the stent to bathe the entire ureter. The usual starting BCG dose is 1/10th standard plus 100 MU IFN-a prepared in a 50 cc saline IV bag. The drug is administered over 2 hours by gravity flow through a micro-drip chamber by placing the suspension at roughly 20-25 cm vertically above the renal pelvis. Full dose BCG is too viscous to flow by gravity through a small stent. Treatments are administered for a total of 6 treatments during the induction cycle. Additional maintenance cycles of 3 sequential treatments have been given to some. One patient treated with a higher dose (1/3) BCG plus IFN-a 100 MU in both sides simultaneously did develop BCG sepsis. After 6 months of appropriate anti-TB antibiotic treatment, therapy at the lower 1/10th dose BCG given one side at a time with a 3 month interval between sides was well tolerated. He is now out almost 3 years with negative cytologies (originally he had pan-urothelial CIS). If treatment intolerance occurs during the induction period, the patient may be given a 2-week rest followed by re-initiation of treatments at a BCG dose of roughly 1/3 that of the prior dose. Similar

2-week delays are permitted for repeat episodes of intolerance. Further BCG dose reduction to 1/100 standard dose is occasionally necessary.

Our preferred method of delivery for those with upper tract TCC involves placing a small (usually 4 French) temporary external stent cystoscopically from the bladder into the mid renal pelvis when possible. This is facilitated either by first placing a .035 angled GLIDEWIRE into the ureter to splint it open and then sliding the 4Fr stent alongside or by placing a .018 angled GLIDEWIRE directly through the 4 Fr external stent. Initially the stent position is marked fluoroscopically for placement into the mid renal pelvis. This mark e.g. 25 cm is then used for subsequent placement without fluoroscopy. The stent is tied to a foley catheter with silk stitches to prevent migration during the 2-hour treatment. The patient is kept supine on a stretcher during this time. After the medication is finished, the foley balloon is then deflated and the stent plus foley removed together. Most patients are discharged immediately to home. If the patient has had bladder intolerance to BCG, a 3-way foley may be placed for light continuous irrigation during upper tract instillation. Conversely, if simultaneous bladder and upper tract therapy is preferred, the foley can be elevated 15-20 cm so that a majority of the upper tract fluid remains in the bladder during the active instillation into the upper tract. All patients are asked to reduce fluid consumption the night and morning before the treatment to minimize excess dilution. Likewise, excessive fluid consumption for the day of the treatment is discouraged.

Frequently Asked Questions

1. What should patients be told about the risk of BCG infection for others?
There has never been a reported case of BCG infection transmitted from a patient receiving BCG bladder cancer therapy to another person. However, since there is the potential for such to occur for immuno-compromised patients, elderly or frail patients, and for infants, good hygienic procedures should be followed. In general, this includes washing the hands, genitalia, and toilet seats with soap and water after voiding as well as application of some form of disinfectant into the toilet bowel for the first few voids. Most commonly, 1/2 cup of bleach is added to the toilet for 15 minutes prior to flushing (caution - this can ruin your septic tank). Other disinfectants such as Lysol or Hydrogen Peroxide may also be suitable. Men receiving BCG therapy should use a condom for 7 days after each treatment while women should generally avoid vaginal contact for 1 week following each treatment.

2. How important is it for patients to keep to a weekly uninterrupted schedule?
The conventional once per week treatment schedule was arbitrarily determined, mostly out of physician and patient convenience without the aid of clinical trial study. Our studies have revealed that waiting up to 2-3 weeks between treatments does not impair the subsequent immune response to the treatment but longer periods might. A small pilot study in Europe has subsequently demonstrated better tolerance with equal efficacy for q 2 wk vs. q wk therapy. Our general practice has been to administer therapy weekly unless there is evidence of intolerance, particularly prolonged cystitis or strong acute symptoms. If either occur we wait at least 2 weeks or until complete resolution. BCG dose may also be reduced depending on symptom severity.

3. How important is it to get through all the scheduled maintenance treatments?
The single most important treatment cycle is the 6-week induction cycle. There appears to be some benefit to getting at least one set of maintenance treatments for many patients with more aggressive forms of bladder cancer but the benefit of prolonged maintenance treatment is unknown. Most patients incur stronger side effects with more treatment cycles. We have used the strategy of BCG dose reduction and treatment delay to minimize these problems. However, if severe intolerance such as persistent cystitis lasting over 2 weeks occurs, it is probably best to forgo further maintenance treatments.

4. Do patients need to rotate from side to side during treatment?
No, there is no evidence that this makes any difference. Nor is there any need to keep the average patient in the office following administration of therapy. Normal ambulation should be sufficient to distribute the medication throughout the bladder surface. The only theoretical concern is for the patient with a dome lesion and air in his/her bladder that could impair BCG contact with this site. For these patients it may be advisable to have them lie prone for 15-20 minutes.

5. I heard that it is advisable to drink lots of fluid following BCG treatment. Is this true?
No, while drinking excess fluid may cut down on the intensity of local side effects there is concern that diluting out the bioactive substances in the urine may also decrease BCG and interferon effectiveness. We recommend normal fluid consumption guided by simple thirst. Caffeine and alcohol should be particularly avoided in the first 12-24 hours post BCG because these substances have irritative and diuretic effects on the bladder.

6. How important is it for a patient to hold the BCG plus interferon in for 2 hours? Will shorter durations work? Should we encourage maximum holding?
No one knows the true answer. Animal studies suggest BCG binding occurs relatively rapidly, even within 20 minutes, whereupon it may persist in a bound or engulfed form for many hours or even days. Interferon-alpha, at the doses used, probably saturates the system relatively quickly but is

flushed out with voiding such that it functionally acts as a pulse therapy. While there is some theoretical advantage to longer dwell time, particularly for interferon, the consequence of forcibly holding in the agents especially at the risk of incurring high-pressure isometric bladder contractions is too dangerous. We specially ask our patients not to go to any extremes to hold their voiding in the setting of severe urgency. For particularly spastic bladders, however, premedication with anti-cholinergics (and even narcotics such as percocet) is very helpful when more conservative measures of fluid restriction and alcohol/caffeine avoidance fail.

7. Is microscopic hematuria or pyuria a contraindication for therapy?

No, microscopic hematuria does not substantially increase the risk of BCG toxicity and may be inevitable due to inflammation and/or tumor bleeding. Only active bleeding or bleeding associated with traumatic catheterization should be used as a basis to defer therapy. There is some recent evidence that >5 WBCs per HPF of UNSPUN urine is associated with a greater chance of toxicity and might be a reasonable basis to delay or reduce the BCG dose. However, in the absence of current symptoms, we do not routinely check urinalysis prior to treatment. If there is a concern for a concurrent bacterial UTI, a urine culture should be obtained, antibiotics started, and treatment delayed.

8. If the patient is not showing signs of BCG intolerance why do you routinely decrease the BCG dose during maintenance therapy and for prior BCG failure patients? Isn't more better?

Paradoxically, higher doses of BCG can actually be immunosuppressive. As a biological response modifier, BCG actually induces a bell-shaped dose response curve whereby only doses within a certain range are optimal. Due to the phenomenon of immune memory, this optimal range actually shifts as the result of prior or concurrent therapy so that lower doses are more effective. Furthermore, interferon-alpha extends this functional dose range for BCG allowing even lower doses to work well.

9. Is it all right to routinely give antibiotics to patients being catheterized for BCG plus interferon therapy?

We do not recommend routine prophylactic antibiotics since they are either unnecessary or potentially harmful. BCG is sensitive to several commonly used antibiotics such as fluoroquinolones (Ciprofloxin, Ofloxin, and Levaquin), doxycycline, and azithromycin. This could impair BCG activity. Conversely, BCG is uniformly resistant to penicillins, cephlosporins, Macrodantin, and Bactrim. If patients require routine prophylaxis for clear indications, such as a cardiac value, then they may receive any of the latter agents. Incidentally, even administration of the TB-specific antibiotic, isoniazid (INH), was not found to reduce the incidence of either local or systemic BCG activity when given the day before BCG treatment through the day after.

10. When is a fever suggestive of a serious condition?

Low-grade fever (less than 101 F) with a sense of chill is common after both BCG and/or interferon therapy. Occasional transient high fever exceeding 102 F with shakes may also occur. Both occur most commonly between 4-8 hours after the BCG instillation. As long as the fever responds to antipyretics such as acetaminophen, aspirin, or NSAIDs, is not associated with systemic deterioration, and does not recur past 24 hours there is little cause for concern. Indeed, such fevers have been reported to be associated with a better cancer response. On the other hand, very high fevers (over 103 F), early onset (usually within 2 hours or treatment), or relapsing evening fevers associated with night sweats suggests a more serious BCG infection and may require immediate hospitalization with institution of appropriate TB-specific antibiotics. For intermediate situations, immediately starting a fluoroquinolone antibiotic may be useful until further follow-up reveals the degree of seriousness of the condition.

11. Are all BCG failure patients the same?

No, we can distinguish at least 5 categories of BCG failures that may ultimately have relevance for clinical therapy: 1) BCG refractory - a patient that has never achieved more than a 6 month reprieve from cancer recurrence after the last BCG treatment cycle, 2) BCG relapser - a patient that has been cancer free after BCG for various periods including a) early relapse - within 1 year; b) intermediate relapse - between 1-2 years; and c) late relapse - beyond 2 years. In general, the longer the interval, the more likely the patient is to respond to BCG plus interferon therapy. There is also a group of patients that fail BCG because they are unable to tolerate the medication. These are referred to as BCG intolerant. Finally, patients may be classified by the number of prior treatment course failures and whether they fail after induction only or during active maintenance.

12. Can the leftover BCG be re-used for the same or different patient?

BCG begins to deteriorate due to clumping or actual death within 2 hours of physical reconstitution/ rehydration. Thus, it should ideally be instilled within 1 hour of preparation. TICE BCG appears to be more labile than TheraCys BCG and a strict time usage within 2 hours should be kept.

13. Is it permissible to use the pre-solubilized liquid form of interferon-alpha in place of the lyophilized powdered form?

We do not recommend this because the liquid form is more dilute and requires a higher volume of liquid to achieve the same interferon-alpha dose (~6 ml vs. 1 ml). Furthermore, the diluent in the liquid solution contains a higher concentration of anti-bacterial substances that could impair BCG viability (and hence effectiveness).

14. Can a double-J stent be used to reflux intravesical therapy into the upper urinary tract for therapy in this site?

Reflux up a double-J stent is not reliable enough to guarantee sufficient prolonged contact of the agent with the tumor. Only if a cystogram reliably shows significant reflux at the volume capacity selected (e.g. 50-100 cc) should this strategy be used.

15. With simultaneous disease in both the upper tract and bladder, which should I treat first? Can I get two for the price of one by treating the upper tract and letting it run down into the bladder?

Generally, treat the worst disease first. For example, a T1 grade 3 cancer in the bladder would take precedence over a positive cytology (no visible lesion) in the upper tract. Unfortunately, by the time fluid instilled into the upper tract has run down into the bladder, it may not be of sufficient potency or concentration to work as a primary inductive therapy. We have had several cases of complete initial response in the kidney but without response to a simultaneous lesion in the bladder. Direct therapy into the bladder did subsequently result in a complete response in the bladder.

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SALVAGE INTRAVESICAL THERAPY WITH INTERFERON-α2B PLUS LOW DOSE BACILLUS CALMETTE-GUERIN IS EFFECTIVE IN PATIENTS WITH SUPERFICIAL BLADDER CANCER IN WHOM BACILLUS CALMETTE-GUERIN ALONE PREVIOUSLY FAILED

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ABSTRACT

Purpose: We determined whether combining low dose bacillus Calmette-Guerin (BCG) interferon-α2B would be effective for patients in whom previous BCG failed.

Materials and Methods: A total of 40 patients in whom 1 (19) or more (21) previous induction courses of BCG failed received 6 to 8 weekly treatments of ⅓ dose (27 mg.) BCG plus 50 million units interferon-α2B. Additional 3 week miniseries of further decreased BCG (1/10, 1/30 or 1/100) titrated to symptoms without changing the interferon-α2B dose were given at 5, 11 and 17 months. In 12 patients a second induction course was given with 1/10 BCG plus 100 million units interferon-α2B. There was multifocal disease in 39 patients, previous BCG had failed within 6 months in 34, disease was aggressive (stage T1, grade 3 or carcinoma in situ in 31, there had been 2 or more previous recurrences in 25 and disease history was greater than 4 years in 13.

Results: At a median followup of 30 months 63% and 53% of patients were disease-free at 12 and 24 months, respectively. 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-α2B 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.

KEY WORDS: bladder, bladder neoplasms, Mycobacterium bovis, interferon alfa-2b

The most efficacious adjuvant treatment for superficial bladder cancer involves successive instillation of live Mycobacterium bovis or bacillus Calmette-Guerin (BCG) into the bladder. However, this treatment fails in 30% to 40% of patients and an additional 30% to 40% of initial responders have relapse within 5 years.[1] Furthermore, when this treatment fails, depending on the degree of bladder cancer aggressiveness patients are faced with the prospect of repetitive surgical procedures, complete bladder removal, treatment with investigational intravesical agents or even high dose chemotherapy and radiation.

Intravesical instillation of the immunostimulant interferon-α2B is less effective than BCG but it has been shown to induce a complete response in up to 40% of patients with superficial bladder cancer, although its durability is limited and most have relapse within 1 year.[2] Importantly as a single agent, it has shown similar efficacy in cases of BCG failure.[3] To our knowledge the exact anticancer mechanisms of action of BCG and interferon-α2B are unknown but involve immune stimulation.

Our hypothesis is that BCG therapy fails in many patients because a sufficiently strong or appropriate cellular immune response to BCG is not mounted. The reason for this abnormal host response is not completely understood but evidence indicates that standard doses of BCG can be detrimental, especially in patients previously BCG immune.[4,5] Furthermore, recently preclinical studies have shown that the cellular response to BCG can be enhanced by the co-administration of interferon-α2B with BCG even at significantly decreased doses.[6] Therefore, we determined whether BCG, appropriately decreased according to previous exposure or intolerance, combined with interferon-α2B for intravesical delivery may salvage cases in which BCG has failed.

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MATERIALS AND METHODS

Between January 1996 and June 1999, 42 consecutive patients with concurrent superficial bladder cancer and relapse after previous BCG therapy were entered into this protocol at Beth Israel Deaconess Medical Center in Boston. Patients excluded from study included 1 who failed to complete therapy due to unrelated cardiac issues and 1 in whom metastatic disease was discovered midway through induction therapy. Of the remaining 30 men and 10 women 43 to 92 years old 19 (48%) and 21 had undergone 1 and 2 or more failed BCG courses, respectively. In most cases there were additional disease characteristics that have been shown in multiple studies to cause a high risk of recurrence and/or progression (table 1). BCG had failed in 34 patients (85%) within 6

TABLE 1. *Risk factors in patients in whom BCG failed*

	No. (%)
Multifocal disease	39 (98)
BCG refractory with recurrence at less than 6 mos.	34 (85)
Aggressive histology (Ca in situ, stage T1, grade 3)	31 (78)
Greater than 2 recurrences	25 (63)
Disease duration greater than 4 yrs.	13 (33)

months after receiving BCG, of whom all except 2 were retreated with BCG plus interferon within 8 months of failure, including 27 within 4 months. In 22 patients cystectomy had already been offered as a therapeutic option.

Induction treatment consisted of 6 to 8 once weekly intravesical instillations of ⅓ standard dose Connaught strain BCG (⅓ of an 81 mg. vial equal to 27 mg. diluted in 50 cc buffered saline) into which 1 cc of freshly reconstituted 50 million units interferon-α2B (Schering-Plough, Kenilworth, New Jersey) were directly added. The choice of 8 induction treatments during the initial half of this study was based on the previously reported favorable results of 8 sequential weekly interferon monotherapy treatments.[3] As it became more apparent that later treatments were associated with greater local side effects in some patients, 6 treatments became standard without any obvious change in clinical efficacy results. The drug mixture was administered within 2 hours of reconstitution. Further dose decreases of BCG in approximately equal gradations of ⅓ (1/10, 1/30 and 1/100) were done as necessary for treatment intolerance by reducing the amount of BCG concentrate delivered into the standard 50 cc buffered saline volume. The interferon-α2B dosing was not altered. Dose delays of up to 2 weeks between treatments were permitted, as was premedication with urinary antispasmodics.

Patients disease-free after completing induction therapy were routinely given maintenance therapy, consisting of 3 weekly miniseries beginning 3 months after the end of induction and repeated twice at further 6-month intervals at approximately 5, 11 and 17 months after the start of induction. A standard maintenance cycle consisted of ⅓ dose BCG plus 50 million units interferon-α2B for dose 1, and 1/10 BCG plus 50 million units interferon-α2B for doses 2 and 3 in that cycle. Further dose decreases and intermittent 1 to 2 week delays in BCG was permitted when there was evidence of BCG intolerance, as defined by fever greater than 102F less than 24 hours in duration, moderate to severe cystitis symptoms persisting beyond 3 days or inability to retain treatment at least 1 hour despite urinary antispasmodics, including narcotics.

Re-induction therapy consisting of 6 weeks of 1/10 dose BCG plus 100 million units interferon-α2B was cautiously administered in 12 patients in whom induction had failed but who initially had less aggressive stage Ta grades 1 to 2 disease but with no progression (4), evidence of improved aggressive features (6) and refused cystectomy for multifocal carcinoma in situ or recurrent T1 grade 3 disease (2) despite counseling. Improvement in these 6 cases involved the resolution of multifocal carcinoma in situ but not papillary transitional cell carcinoma in 4, resolution of stage T1 grade 3 disease but not multifocal carcinoma in situ in 1 and evidence of only focal residual carcinoma in situ in 1. Three improved patients ultimately achieved a complete and durable response, while 1 patient in each of the other 2 categories also became disease-free. Maintenance courses consisted of 1/10 BCG plus 100 million units interferon-α2B given in 3 weekly miniseries as described with the BCG dose decreased as appropriate for intolerance.

Patients were evaluated 6 to 8 weeks after completing the induction cycle with cystoscopy, biopsy and cytology. Thereafter they were followed for the initial 24 months with cystoscopy every 3 to 4 months with cytology and biopsy as appropriate, and every 6 to 12 months thereafter. Median followup for the group overall was 30 months (mean 31, range 15 to 52). No patient was lost to followup.

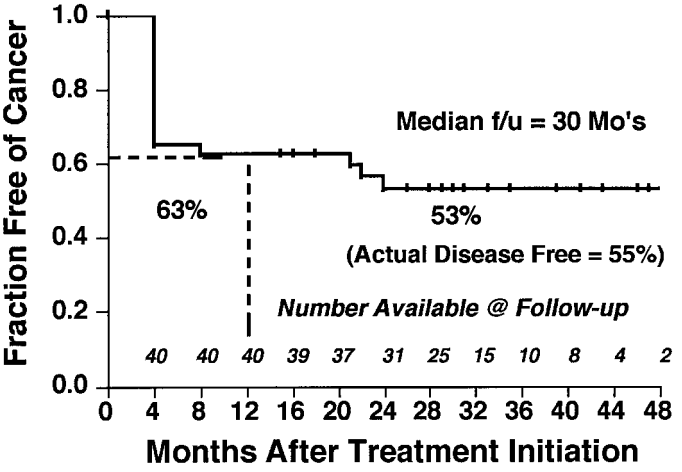
RESULTS

Treatment efficacy. Overall this combined regimen of intravesical low dose BCG plus interferon-α2B resulted in 63% 12-month and 53% 24-month freedom from bladder cancer recurrence based on Kaplan-Meier analysis (see figure). Long-term responders included 5 of 12 patients (42%) given a second induction cycle. The 12 and 24-month disease-free rates for 1 induction cycle alone were 56% and 48%, respectively. At the current 30-month median followup 22 patients (55%) remained disease-free. Interestingly there have been no relapses after 24 months. No patient who received all 3 scheduled maintenance cycles has had recurrence. Of the initial 22 patients recommended for cystectomy 12 (55%) remained disease-free with a normally functioning bladder.

Of the 18 recurrences 14 (78%) were detected at initial cystoscopy. In 5 cases muscle invasion was present, permitting early referral to more aggressive options such as cystectomy and/or chemotherapy plus radiation. Six patients had recurrent carcinoma in situ, of whom 2 elected cystectomy. Another patient elected cystectomy for recurrent stage T1 grade 3 and the remaining 2 had recurrent infrequently low grade, low stage tumors. None of these patients with early failure have had metastasis or died of bladder cancer, although 2 with no evidence of disease died and another died with disease but of unrelated causes. There have been 4 late recurrences at 8, 21, 22 and 24 months, respectively. In 2 cases low grade, low stage recurrence was accessible to local transurethral bladder resection. The other 2 cases presented as disease outside of the bladder with bilateral positive upper tract cytology and upper tract infiltrative transitional cell carcinoma with metastasis, respectively.

Tables 2 and 3 list responses by disease characteristics. While insufficient sample size and lack of strict comparison groups did not permit meaningful statistical evaluation, there were no obvious differences in response according to stage, grade or coexistent carcinoma in situ (table 2). Similarly in other defining disease parameters there were no gross differences according to tumor aggressiveness, number of previous recurrences or number of previous failed BCG cycles (table 3). There appeared to be a trend toward a lesser response in patients with a previous relapse within 6 months of BCG or disease for greater than 4 years but not enough to permit definitive conclusions to be drawn.

Treatment tolerance. The side effects attributable to combined low dose BCG plus interferon-α2B were generally the same types associated with BCG therapy alone, including local cystitis, transient hematuria, flu-like symptoms and fever. None of these side effects was of sufficient magnitude initially to cause any patient to avoid the first maintenance cycle. However, these symptoms tended to peak during the treatments 2 or 3 during the maintenance cycles, resulting in progressive patient withdrawal from further therapy. Even after BCG dose reduction and temporary delay treatment



Cancer-free survival of patients in whom BCG failed after BCG plus interferon-α2B treatment. *f/u*, followup.

TABLE 2. *Breakdown by highest stage, grade and coexistent carcinoma in situ*

Stage	No. (% 2-yr. no disease evidence)
Ta:	17 (64)
Ca in situ	8 (75)
No Ca in situ	9 (56)
T1 (grade):	13 (54)
3, Ca in situ	9 (67)
2, Ca in situ	2 (0)
3, no Ca in situ	1 (0)
2, no Ca in situ	1 (100)
Isolated Ca in situ:	10 (40)
With papillary transitional cell Ca	19 (63)
Any Ca in situ	29 (54)

TABLE 3. *Disease-free status by dichotomous tumor characteristics*

Subgroup	No.	% 12 Mos.	% 24 Mos.	Actual %
Overall	40	63	53	55
Failure:				
1	19	63	52	53
2+	21	62	55	57
Aggressive:				
No	9	67	56	56
Yes	31	61	53	55
Recurrence:				
2	15	53	44	47
Greater than 2	25	68	54	56
Relapse:				
Late	6	83	83	83
Early	34	59	48	50
Disease duration (yrs.):				
Less than 4	27	67	58	59
Greater than 4	13	54	43	46

was discontinued due to intolerance in 3 patients during maintenance cycle 2 and in another 6 during maintenance cycle 3. Overall 46% of patients eligible for 3 cycles of treatment received all 3 (table 4). An additional patient was withdrawn from treatment during the second maintenance cycles for genuine BCGosis with granulomatous hepatitis that required 6 months of antituberculotic therapy with isoniazid and rifampin. Another 3 patients withdrew for reasons unrelated to treatment tolerance. Overall 10 of 25 patients (40%) had toxicity sufficient to terminate scheduled maintenance treatments prematurely.

DISCUSSION

Immunotherapy with BCG has consistently resulted in an initial complete response rate of 55% to 65% for papillary tumors and 70% to 75% for carcinoma in situ.[1,7] Long-term studies have documented benefits in terms of decreased recurrence, progression and cystectomy rates, and even improved survival.[8] However, despite the good response to BCG therapy almost 50% of cases ultimately fail BCG within 5 years, highlighting the need to discover salvage methods.[1,9]

The usefulness of repeat BCG courses, chemotherapy or alternative immunotherapy for salvaging BCG failure is limited (table 5).[10–13] Catalona et al noted that a third course of BCG was effective in only 20% of patients.[10] Likewise salvage chemotherapy is minimally effective. In a study of 21 patients in whom 1 course of BCG failed only 4 (19%) were disease-free at 3 years with mitomycin.[11] In the pivotal trial leading to Food and Drug Administration approval for valrubicin, an anthracycline derivative with higher lipid solubility, 19 of 90 patients (21%) at high risk treated once weekly for 6 weeks were disease-free at 6 months.[12] With subsequent followup fewer than half remained disease-free at 2 years. Interferon-α2B monotherapy has also been administered in cases of BCG failure with limited success. In a small series the 1-year disease-free rate was approximately 18% for carcinoma in situ and papillary disease.[3] In a trial in which thirty-four patients with carcinoma in situ patients underwent at least 2 cycles of failed BCG 4 (12%) had no evidence of disease for greater than 33 months. However, all previous BCG refractory cases of carcinoma in situ relapsed within 6 months.[13]

TABLE 4. *Maintenance therapy*

Cycle	No. Eligible	% Receiving	Reason Not Received
1	26	100	Not applicable
2	25	76	1 Refusal, 1 other medical, 3 intolerance, 1 BCGosis
3	24	46	1 refusal, 6 intolerance

To our knowledge the cause of BCG ineffectiveness is unknown but several explanations are possible. Disease recurrence may result from under staging of occult muscle invasive disease, which develops in up to 30% to 40% of stage T1 grade 3 cancer cases.[14] This situation can be minimized by careful repeat resection with adequate sampling of underlying muscle. A large tumor burden of greater than 2.5 cm. also increases the risk of failure, highlighting the need for as complete tumor resection as possible.[15] Conceivably the failure of BCG to bind to fibronectin receptors in the bladder may be responsible.[16] Whether there are tumor characteristics that define intrinsic resistance to immunotherapy mechanisms is unknown since to our knowledge no morphological, biochemical or genetic features have yet been identified. A final provocative explanation of why BCG therapy fails is that there is no adequate or appropriate immune response. At several laboratories results have shown a higher probability of success in patients with urinary cytokines, such as interleukin (IL)-2, and/or interferon-γ or lesser amounts of IL-6 and serum antibodies to BCG heat shock proteins, features that are usually associated with a specific immune response known as T helper type 1.[17–21]

Recently many preclinical studies have shown synergy between BCG and interferon-α2B. Pryor et al reported that when mixed they inhibit transitional carcinoma cell line growth in culture better than either alone.[22] Similar synergy has been observed for interferon-α2B mixed with the BCG induced cytokines interferon-γ and/or tumor necrosis factor-α for making transitional cell carcinoma cells better potential targets for immunotherapy or decreasing tumor angiogenesis.[23–26] Luo et al noted that interferon-α2B may profoundly enhance and polarize the human BCG immune response toward the T helper type 1 pathway by decreasing inhibitory IL-10 production.[6] It was especially evident at lower BCG concentrations and in patients with immune anergy from BCG over treatment. Animal bladder cancer trials of interferon-α plus BCG have also shown higher effectiveness than BCG alone.[27–29]

Clinical trials of combination BCG plus interferon-α2B intravesical therapy are still in their relative infancy. Downs et al reported that the agents are physically biocompatible.[30] Bercovich et al assessed ½ dose BCG plus 10 million units interferon-α2B for prophylaxis against papillary bladder tumor recurrence and observed efficacy equal to that of full dose BCG but with improved tolerability.[31] Stricker et al completed a phase I clinical study involving 12 patients, including 8 with carcinoma in situ, adding interferon-α2B to ½ dose BCG.[32] The response rate at 12 months was 92%, including 75% and 15% complete and partial responses, with excellent tolerability using variable doses of 10 to 100 million units interferon-α2B. Esuvaranathan et al reported preliminary results of a 3-arm prophylactic study after transurethral bladder resection with standard dose BCG, ⅓ dose BCG, and ⅓ dose BCG plus 10 million units interferon-α2B in a 6 + 3 format.[33] The 19-month recurrence rate was 50% for standard BCG, 30% for ⅓ dose BCG and only 10% for the combined treatment. We have treated 22 additional high risk

TABLE 5. *Efficacy comparison with historical series*

References	Agent	Pt. Group	No. (% 2-yr. no disease evidence)
Catalona et al[10]	BCG cycle 3	Mixed	6 (20)
Williams et al[13]	Interferon-α2B	Pure Ca in situ	34 (12)
Malmstrom et al[11]	Mitomycin C	Mixed, 1 BCG failure, crossover	19 (23)
Steinberg et al[12]	Valrubicin	Ca in situ, all concurrent papillary transitional cell Ca resected	90 (8)
Present series	BCG, interferon-α2B	Mixed, 2 or more BCG failures	21 (55)

cases that were not BCG failures (BCG naive) with combined therapy comprising standard dose BCG during induction plus 50 million units interferon-α2B and achieved 68% 2-year median disease-free survival (O'Donnell, unpublished data). We have not advocated lower dose BCG in this subgroup during induction due to inferior results previously reported by Morales et al for ⅓ dose BCG versus standard dose BCG in a North American cohort of patients that had presumably not been BCG sensitized by previous BCG vaccination or tuberculosis exposure, which is common elsewhere in the world.[34] However, to our knowledge this report represents the first test of combined therapy specifically for previous BCG failure.

Our protocol design was based on several considerations, including the improved response in previously BCG sensitized patients with lower dose BCG therapy,[5] the independent single agent activity of at least 50 million units interferon-α2B versus 10 million units[2] and the recognized value of miniseries BCG maintenance therapy.[35] We added the practice of BCG dose de-escalation or titration and we limited total maintenance cycles to 3 based on the inability of most patients to endure this degree of repetitive stress. However, while tolerance was generally good initially, only about half of the patients scheduled to receive 3 maintenance cycles received all 3, a result similar to that in the Southwestern Oncology Group 8507 trial. Despite important dose decreases it is not clear why a higher maintenance retention rate was not achieved. It was likely partially due to our heavily BCG pretreated cohort, in which 3 to 5 courses had already failed in some patients. It is also possible that even more rapid BCG decreases during maintenance would have been advantageous. In a subgroup of patients we measured urinary cytokine and noted that moderate but not intolerable symptoms were associated with more sustained urinary interferon-γ, of which the full significance has not yet been explored (unpublished data). Only 1 serious adverse event (BCGosis) occurred, which responded well to conventional therapy.

Our results show that even in patients at high risk for recurrence or progression 55% can be rendered disease-free for a substantial period. While further followup is required, it is encouraging that no recurrence has yet been observed after 24 months or in patients completing all 3 planned maintenance cycles. A high response was evident even in patients previously deemed refractory to BCG, as defined by recurrence within 6 months of previous BCG, and in those already counseled to undergo cystectomy. Surprisingly even patients in whom 2 or more previous courses of BCG had failed appeared to benefit as well as those with 1 previous failed course. However, this result may also have been due to selection/referral bias since patients with worsening disease may already have been directed toward more radical therapy. While we realize the difficulty in comparing historical series, our results appear favorable compared with other treatments in similarly categorized cases (table 5).[10–13]

The decision of how to treat patients after BCG failure must be individualized based on intrinsic tumor risk, failure pattern, co-morbidity and patient preference. In patients at high risk for disease progression, such as those with stage T1 grade 3 tumors with carcinoma in situ and failure immediately after 1 cycle of BCG radical treatment must be considered early. Conversely in patients with recurrent stage Ta, grades 1 to 2 tumors many other conservative options may be explored without great fear of jeopardizing survival. An analysis of the type of BCG failure may also important. Cases that never achieve disease-free status greater than 6 months in duration or fail on active maintenance have been shown to be less likely to benefit from repeat BCG therapy than those of later relapse.[36] Interestingly combined BCG plus interferon-α2B appears to salvage many refractory cases. It has also been suggested that cases of BCG relapse and tumors that have increased in stage, grade or positive cytology, or are p53 positive may deserve more aggressive action.[9, 37, 38] The role of combined therapy in this group has not been completely defined. Unfortunately even with appropriate guidelines some patients with locally advanced superficial disease are not candidates for radical surgery due to comorbid medical illness. Others frankly refuse to consider losing the bladder even after extended discussions of risk. In all of these circumstances alternative conservative measures may be appropriate.

Further studies are clearly needed to define the best candidates for combined BCG plus interferon-α2B therapy. A larger phase II trial to examine subgroup characteristics has recently achieved its accrual goal of 1,000 patients (unpublished data). Phase III trials comparing BCG to BCG plus interferon-α2B for BCG naive and first-time BCG failure patients are being developed. Until then, patients at high risk in whom BCG fails must be carefully selected. In others it may be best to administer this treatment before the point at which radical therapy may first be considered. On a cautionary note, patients with high risk characteristics in whom combined therapy fails early remain at increased risk for local progression. Those with later failure should also be assessed for disease outside of the bladder vault.

CONCLUSIONS

Combined intravesical low dose BCG plus interferon-α2B appears to be effective in many patients at high risk for disease recurrence and/or progression previously deemed BCG refractory. While no obvious defining criteria for treatment nonresponse was evident in our relatively small study, we cannot completely rule out intrinsic biases that may occur in a single institutional study. Larger multicenter trials with even longer followup are required to validate these initially encouraging results to ensure that these patients are effectively spared radical surgery and cystectomy is not simply being delayed. However, early failure on this regimen implies intrinsically resistant disease that should be aggressively pursued using more radical treatment options.

Tracy Downs assisted with patient care and Randall Eaton maintained the database.

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EDITORIAL COMMENTS

Immunotherapy with intravesical BCG can provide effective treatment for superficial bladder cancer. It is the international standard for carcinoma in situ and is often used as initial therapy for papillary bladder cancer. Despite its extensive use the intravesical administration of BCG remains rooted in empiricism. These authors report a small, single institution experience using a novel approach to intravesical immunotherapy based on preclinical work showing an enhanced immune response with combined BCG and interferon-α. Conveniently these 2 drugs can be mixed together and instilled simultaneously. This initial study using various doses of BCG and interferon-α evaluated 19 patients in whom 1 induction course of BCG had failed and 21 in whom 2 or more courses of BCG had failed. Patients were treated with an induction course of BCG and interferon-α followed by maintenance therapy. A second induction course was administered in 12 patients in whom BCG/interferon-α induction failed. The dose of BCG was decreased to adjust for toxicity. At a median followup of 30 months the 2-year disease free response rate for 1 induction was 48%. This response rate increased to 53% with a second induction. Patients with papillary transitional cell carcinoma and carcinoma in situ had a better 2-year disease-free response rate (63%) than those with isolated carcinoma in situ (40%).

Intravesical therapy continues to be an important method of treating patients with bladder cancer that does not invade the muscularis propria. The obvious advantages of effective intravesical therapy are disease control and retention of a functional bladder. The risk of

continued (salvage) intravesical therapy for stage T1 or carcinoma in situ recurrence is disease progression. Two additional patients were enrolled but excluded from study. One of them had metastatic disease midway through induction therapy. This infrequent event (1 of 42 cases) does not condemn this approach. However, physicians and patients must be aware that salvage intravesical therapy can be associated with risks far greater than local toxicity.

This promising initial study has translated laboratory observations to the clinic. While the data are encouraging, the concluding words of the authors should be heeded. "Larger multicenter trials with even longer followup are required to validate these initially encouraging results."

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The authors pursued a bladder sparing strategy in patients with superficial bladder tumors in whom BCG therapy failed. The results suggest that combining low dose BCG plus interferon-α2B may salvage some BCG failures. Does the number of patients, study design, definition of high risk tumors and length of followup justify such a cautiously optimistic conclusion?

Only 40 patients were treated and followed a median of 30 months (range 15 to 52). Few patients followed less than 5 years are probably insufficient, although it is encouraging that no relapses were reported beyond 24 months. The original BCG trials tested BCG as an adjunct to surgery. They required patients to undergo complete transurethral resection (we do not know whether it was done here) followed by 6 weeks of BCG therapy. The response to BCG was evaluated by repeat transurethral resection and urine cytology at 3 and 6 months because this regimen allowed sufficient time for BCG to eradicate subclinical disease, particularly carcinoma in situ, and 2 transurethral resection biopsies provided a more accurate evaluation of the BCG effect (as well as therapy) than just 1 at 3 months (reference 37 in article). In the current study 85% of patients were deemed BCG refractory (48% after 1 course of BCG) because of tumor recurrence in less than 6 months. Further followup and repeat transurethral resection may have converted some of these failures into successes. Do the patients have high risk tumors? Nine patients had low grade, albeit recurrent stage Ta tumors and 10 had isolated, probably focal carcinoma in situ, suggesting that 48% of the 40 had disease at low risk for progression. Thus, the conclusion that BCG plus interferon-α may rescue many patients who never achieve disease-free status for longer than 6 months with BCG alone must be tempered by the small number treated, short followup and confounding variables regarding patient selection.

Long-term (15-year) studies show that many patients with refractory superficial bladder tumors are treated conservatively for too long, risking tumor progression and decreased survival even with cystectomy. The key question facing urologists and patients is when to abandon local therapy in favor of cystectomy. The authors are attempting to delay and perhaps even prevent cystectomy in some patients by better local control of recurrent nonmuscle invasive disease and their early results deserve attention. Sparing the bladder is the desired goal of each patient as long as it does not unduly risk survival. The authors are urged to test this regimen in more patients but more importantly to provide long-term survival results in treated patients.

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Because BCG is undoubtedly an effective therapy for prevention of bladder tumor recurrences but there is also clearly room for improving its use, BCG therapy deserves more investigations and refinements.[1] There are many avenues to investigate from defining the optimal BCG regimen to reconsidering doses and schedules but also optimizing its action.

Recombinant techniques helping to produce BCG mycobacteria secreting various cytokines (mainly involved in Th1 differentiation) is an exciting new way method.[2] Recombinant BCG vaccines expressing secretory proteins from M. tuberculosis have been demonstrated to induce greater protective immunity against tuberculosis than conventional BCG vaccines.[3] Similarly, combining BCG with cytokine instillations, such as interferon-α2B, may decrease BCG dose as well as its side effects. It may also hypothetically increase its efficacy. BCG works as an immunotherapy and has been demonstrated to elicit different kinds of immune responses locally but also on a systemic level involving mainly Th1 cytokines.[4,5] Alternating BCG with those cytokines known to be involved in its mechanism of action makes sense.

The present study, although preliminary, is interesting in many aspects. The authors demonstrate that some patients in whom BCG failed might respond to the combination of low dose BCG plus interferon-α, and, thus, be spared radical cystectomy. Of course, longer followup is needed and the ultimate ability of BCG to prevent muscle invasive disease long term is not warranted.[6] With 53% of patients in whom BCG failed were disease-free at 24 months, this combination of BCG plus interferon-α2B clearly supersedes previous other second line therapy.

The second interesting aspect is related to the BCG dose reduction. To decrease side effects many authors have tried to decrease BCG doses to half or a third of the dose.[7] Some authors have even hypothesized that when too much BCG is given, an inadequate immune response is generated (Th-2 type with IL-4 and IL-10 cytokine production) and BCG might be less effective.[8] We should not forget that when Morales discovered the use of BCG intravesically, he asked the BCG manufacturer to send him a few vials of vaccine. He received and used 6 bottles (Morales, A.: personal communication), thus introducing somehow by pure chance the schedule and BCG doses.

The idea of decreasing BCG doses for maintenance therapy to one-tenth or even one-thirtieth of the initial dose is worth pursuing and again makes sense since these patients were already sensitized. However, it is not known whether this BCG regimen and maintenance dose will be adequate as a first line therapy. An intriguing point in the present study is that despite important reductions in dosage in the maintenance phase, side effects were still frequent.

The present study further demonstrates that BCG therapy deserves continuous studies. The 6 or 8 weekly BCG courses using high doses are far from optimal for all patients. Tailoring BCG treatment according each individual depending on immunological status, previous sensitization to mycobacteria or the type of immune response mounted is 1 method. Further expanding Th1 responses using a combination of BCG plus intravesical cytokines is another interesting method certainly worth further investigations.

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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, and William C. DeWolf, Boston, MA. (Presented by Dr. O'Donnell).

INTRODUCTION AND OBJECTIVE: 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 (IFN-α) 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-α. 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-α 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-α 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.

CONCLUSION: Combination intravesical low-dose BCG + IFN-α 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.

Funding Source: None

760

AN EVALUATION OF BCG PLUS INTERFERON-ALPHA-2B TOXICITY IN A NATIONAL MULTICENTER PHASE II TRIAL

Michael A Odonnell, Kaye Hartman, National Phase Ii Bcg/ifn-Alpha investigator group, Iowa City, IA*

INTRODUCTION AND OBJECTIVES: To determine the incidence of serious adverse events (SAEs) in a large ongoing national study of intravesical BCG plus IFN-α and compare this to the reported incidence from previous BCG monotherapy studies.

METHODS: From May, 1999 to January, 2001 1100 patients were recruited into a multicenter US trial. Patients were administered 50 MU IFN-α and full dose BCG if they were BCG naive (56%) or 50 MU IFN-α plus 1/3 dose BCG if they had previously failed BCG monotherapy (44%). Additional maintenance treatments consisting of three separate 3-week mini-series of further reduced dose BCG (1/3rd-1/10th-1/10th) plus 50 MU IFN-α were provided at 5, 11 and 17 months. 10% of patients received a 2nd re-induction course (100 MU IFN-α + 1/10th BCG) for tumor recurrence at 3 months.

RESULTS: Adverse events were categorized as described in a 2606 patient BCG monotherapy summary report (Lamm, et al. Prog. Clin. Biol. Res. 310: 325-34, 1989). Additional SAEs for combination therapy included 10 cardiac events (ischemia, CHF, arrhythmia), 8 of which were felt to be unrelated to the drugs by the site investigators; 6 reversible neurological events (confusion, TIA/CVA, weakness) and 4 miscellaneous events. The mean number of BCG + IFN-α treatments/patient was 10.

CONCLUSIONS: Combination BCG plus IFN-α displays an acceptable level of serious toxicity in comparison to previous reports on BCG monotherapy. Furthermore, patients previously failing on BCG monotherapy do not appear to be at any substantially increased risk for serious toxicity.

SAE	BCG + IFN-α (n=1100)	BCG (n=2606)
Fever	2.4%	2.9%
Prostatitis/Epididymitis	0.4%	1.3%
BCG-osis/itis	0.7%	0.7%
Arthralgia/Arthritis	0.3%	0.5%
Severe Hematuria	0.5%	1.0%
Rash	0.2%	0.3%
Contracted Bladder	0.2%	0.2%
Renal Abscess	0.1%	0.1%
Sepsis	0.1%	0.4%

765

BACILLUS CALMETE-GUÉRIN PLUS INTERFERON ALFA 2B INTRAVESICAL THERAPY MAINTAINS AN EXTENDED TREATMENT PLAN FOR SUPERFICIAL BLADDER CANCER WITH MINIMAL TOXICITY *John S Lam*, Mitchell C Benson, New York, NY; Michael A O'Donnell, Iowa City, IA; Alexandra Sawczuk, Hackensack, NJ; Anna Gavazzi, Michael Wechsler, New York, NY; Ihor S Sawczuk, Hackensack, NJ*

INTRODUCTION AND OBJECTIVES: Bacillus Calmette-Guérin (BCG) and interferon alfa 2B (IFN-α2B) have both been individually used for the intravesical treatment of superficial bladder cancer. We report our experience on the therapeutic efficacy and toxicity of BCG combined with IFN-α for treating superficial bladder cancer, including those patients that had failed previous BCG therapy.

METHODS: Thirty patients with superficial bladder cancer underwent treatment with full-, 1/3-, or 1/10-dose of BCG plus 50 or 100 MU of IFN-α2B based on prior BCG exposure and tolerance, given weekly for 6 weeks. Patients with no evidence of cancer proceeded onto maintenance therapy of 3 weekly treatments at 3 months followed by two additional maintenance cycles given 6 months apart. Response was assessed by cystoscopy/biopsy every 3 months following treatment.

RESULTS: Eighteen patients had previously failed intravesical BCG induction therapy. Prior to BCG plus IFN-α2B treatment, 26 patients had aggressive disease (stage T1, grade 3, or carcinoma in situ), 24 had recurrent disease, and 4 had disease of over 4 years duration. Combination BCG plus IFN-α2B intravesical therapy was well tolerated. Twenty-two patients (73%) remain disease-free and 8 patients (27%) had disease-recurrence at a median follow-up of 10 months. Five of 8 patients (63%) ultimately failing combination therapy did so at the first 3-4 month evaluation. Six of 8 patients (75%) benefited from a 2nd induction course.

CONCLUSIONS: Combination intravesical BCG with IFN-α2B therapy is an effective and tolerable alternative for patients with superficial bladder cancer. However, radical treatment options should be pursued for early failures of this combination regimen.

COMBINATION BCG PLUS INTERFERON-ALPHA FOR PRIOR BCG FAILURES: EARLY RESULTS FROM A NATIONAL MULTICENTER STUDY

O'Donnell, Michael A, MD. Iowa City, Iowa

Results from several small single institution trials have suggested combination immunotherapy with intravesical BCG plus interferon-alpha (IFN-α) can salvage a significant percent of patients previously failing BCG monotherapy. This report provides the results from 301 evaluable patients enrolled from 125 sites with median follow-up of 18 months.

The patient profile consisted of 50% stage Ta, 22% T1, 21% pure CIS and 7% mixed papillary transitional cell carcinoma (pTCC) + CIS. 78% were of intermediate to high grade and 42% had failed 2 or more prior courses of BCG. 38% had also failed prior chemotherapy.

Nearly all (95%) of patients were treated with a 6-week induction course of 1/3 standard dose BCG plus IFN-α-2B 50 million units (MU) per instillation. Prior BCG intolerant patients (5%) were started on 1/10 BCG + 100 MU IFN-α. Complete responders received additional 3-week maintenance cycles at 3, 9, and 15 months post induction. Efficacy was assessed by quarterly cystoscopy and cytology/biopsy as appropriate. Tolerance was measured with a daily symptom questionnaire and toxicity estimated using weekly physician determined toxicity scales.

The Kaplan –Meier calculated freedom from disease rate for the entire group at 24 months was 45%. Factors associated with a better response included: pTCC +/- CIS, higher grade, size < 2.5 cm, solitary tumor or tumor number < 5, no residual disease, <5 prior tumor resections and <3 prior chemotherapy cycles. Factors trending to be associated with a worse outcome included prior failure while on BCG maintenance, earlier time to prior BCG failure, and prior chemotherapy. Factors not associated with response were age, gender, BCG strain (Tice or Connaught), tumor architecture, prior IFN-α failure, prior courses of BCG, and stage T1 vs. Ta (prior or current). Only 6.1% have progressed to date.

Toxicity was modest with 23% experiencing moderate to severe symptoms, 15% using medications for symptoms, 5% delaying treatments and/or further dose reducing BCG, and 2.9% omitting some treatments. Serious adverse events (SAEs) occurred in 5% of patients most of which (3%) were related to BCG infection. A total of 11% dropped out due to either SAEs or intolerance, results quite comparable to historical standard dose BCG monotherapy trials.

This multicenter trial substantiates the previous encouraging reports of the efficacy of combination BCG + IFN-α as salvage therapy for patients with moderate to high risk superficial bladder cancer previously failing BCG alone with a high level of patient tolerance and minimal serious toxicity.

PRESENTED MARCH 11, 2003 AT THE INTERNATIONAL BLADDER SYMPOSIUM, ARLINGTON, VA

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INTERIM RESULTS FROM A NATIONAL MULTICENTER PHASE II TRIAL OF COMBINATION BCG PLUS INTERFERON-ALFA-2B FOR SUPERFICIAL BLADDER CANCER

Michael A. ODonnell*, Iowa City, IA; Kathleen Lilli, Iowa City, IA; Christina Leopold, Iowa City, IA

Introduction and Objective: This report provides interim results from a large multicenter trial of combination BCG plus interferon alfa-2B (IFN) for both BCG naive (N) and previous BCG failure (F) patients with superficial bladder cancer (SBC).

Methods: 337 evaluable patients with moderate to high risk SBC (83% grade 2-3, 70% recurrent, 55% multifocal, 49% stage T1 or CIS) enrolled from May 1999 to May 2000 with median 24 months follow up are included for analysis. BCG N patients (n=206) were treated with a 6-week induction course of standard dose BCG plus 50 million units (MU) of IFN followed by three 3-week maintenance cycles of reduced dose BCG (1/3-1/10) plus 50 MU IFN at 3, 9, and 15 months post induction. BCG F patients (n= 131) were treated similarly excepting induction therapy began at a reduced (1/3-1/10) BCG dose plus 50 MU IFN. Patients were evaluated for recurrence with quarterly cystoscopy + cytology and biopsy/resection as appropriate. Patient tolerance was assessed with a daily symptom questionnaire and toxicity estimated using a weekly physician determined toxicity scale.

Results: The simple tumor recurrence rates for BCG N and BCG F patients were 35% and 53%, respectively. The Kaplan-Meier estimates for freedom from disease were 71%, 61%, and 58% for BCG N patients at 1, 2, and 3 years. The corresponding results for prior BCG F patients were 53%, 40% and 40%. Female gender, age <50 or >70, and papillary-only disease were associated with greater recurrence in BCG N patients while multifocality, complete lack of prior BCG response, duration > 2 years and CIS were adverse prognostic factors for prior BCG failures. During the induction phase, moderate to severe local symptoms were present in 6% (N) and 17% (F). Toxicity-related premature dropout; treatment delay and/or further BCG dose reduction; and need for symptomatic drugs were 3.7%, 3.5% & 13% during BCG N and 7.3%, 4.3% & 16% during BCG F induction treatments. Moderate-severe systemic side effects were uncommon (1.8% and 5.6%, N vs. F). Symptoms and toxicity remained relatively constant during maintenance therapy for BCG F but increased to a commensurate level for BCG N patients.

Conclusions: This multicenter trial substantiates the previous early encouraging reports of the efficacy of combination BCG + IFN as upfront and salvage therapy for patients with moderate to high risk SBC with a high level of patient tolerance and minimal serious toxicity. While this study is still immature, tumor recurrences in the first year following protocol completion appear rare.

Source of Funding: Schering

SUO 3rd Annual Meeting Bethesda, MD

Combo drug treatment works for bladder Ca BCG failures

Prior BCG courses do not affect combo effectiveness; best results seen in high-grade Ta/T1

Bob Roehr
UT CORRESPONDENT

Bethesda, MD—A combination of low-dose bacille Calmette-Guérin and interferon-alpha (IFN-α) has shown promise in the treatment of bladder cancer patients who have failed initial treatment with BCG.

"We estimate that there are at least 50,000 patients circulating in the system annually that are BCG failures," said Michael O'Donnell, MD, associate professor and director of urologic oncology, University of Iowa, Iowa City. "We sometimes forget that patients with superficial bladder cancer live a long time, so there is a prevalence of about 600,000 total cases in the system."

Dr. O'Donnell

He presented his team's data of a national phase II trial at the annual Society of Urologic Oncology meeting here.

45% free of disease

Dr. O'Donnell said that the phase II trial enrolled 1,106 patients at 125 sites between May 1999 and January 2001, of which about 42% were prior BCG failures. About two-thirds of the enrollees have completed one induction cycle of therapy, with median follow up of 18 months. Some 80% of the patient population is at community-based sites, so the outcome is likely to be representative of real world conditions, he said.

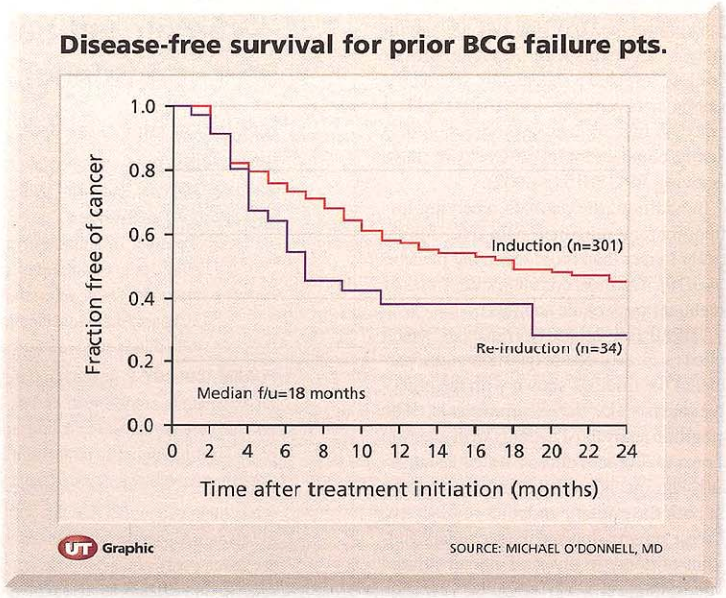
The median age at enrollment was 72, with a male-to-female gender ratio of 3:1, which is representative of disease occurrence. About half were stage Ta; 22% were T1; 21% were "pure carcinoma in situ;" and 7% were mixed pTCC plus CIS.

Of these patients, 78% had an intermediate- to high-grade tumor ratio of 1:1.6, and about 38% had failed prior chemotherapy. Twenty-seven percent have had sustained disease for over 2 years.

Patients who had previously failed BCG were given an induction phase of a 1/3 dose of BCG+IFN-α (50 MU) for 6 weeks. About 5% of the patients were deemed intolerant and went on a regimen of 1/10 dose BCG+IFN-α (100 MU) for 6 weeks.

The maintenance phase was three cycles of 3 weeks duration administered at 3, 9, and 15 months after completion of the induction phase. There are provisions for dose reduction and delay for those experiencing difficulty with the regimen. Some 5% experienced serious adverse events, and the dropout rate due to treatment intolerance was 11%.

Data on 301 evaluable patients at 24 months showed 45% of patients are free of disease by all criteria. A group of 34 patients had failed within 3 months and were allowed to repeat the induction cycle. They showed a reduced—but still substantial—28% 24-month durable response on the second round, Dr. O'Donnell said.



One of the factors associated with better response in all patients was papillary TCC (pTCC) with or without CIS. Dr. O'Donnell said he was surprised to see that, with "pure CIS," the response to combination therapy was less than the response to first-time use of BCG monotherapy.

"High-grade Ta and T1 disease performed identically in the combination therapy. The curves are superimposed," he said.

No difference in number of failures

Initial studies suggested that failing two or more courses of BCG would be predictive of failure with this combination. But that did not hold true in the larger study, Dr. O'Donnell said.

"There is no difference between failing one, two, three, or more courses of BCG," he said. "Another interesting surprise is that low-grade Ta performed worse than high-grade Ta and T1. This supports some of our clinical anecdotes and observations that the nuisance small tumors are sometimes the most difficult to eradicate."

Tumors of <2.5 cm all followed the same favorable response curve, while those >5 cm clustered along the lowest response curve, explained Dr. O'Donnell. A smaller number of tumors correlated with a better response to therapy.

Over a quarter of the study population had five or more previous interventions (ie, transurethral resections) and "a statistically significant decrease in the effectiveness of combination therapy," Dr. O'Donnell said.

Tumors should be resected to completion, and they were in 95% of the patients, he said. But that was not the case with 10 patients, and Dr. O'Donnell could see "a clear early drop off and a low response" in those patients.

Other factors showing a trend toward predicting a worse outcome were multiple prior failures to chemotherapy and early (within 6 months) failure of prior BCG or failure while on prior BCG maintenance therapy.

"A lack of statistical significance here doesn't mean a difference doesn't exist," Dr. O'Donnell warned. "For instance, most of the early BCG studies that looked at prevention of progression did not show statistical significance. It was only when you powered the study large enough with a meta-analysis that you could see a decrease in progression."

Perhaps there is something about previous chemotherapy that leads to less responsiveness to the BCG+IFN-α combination, he suggested.

"Patients who have had cancer for less than 2 years or greater than 4 years seem to perform the same. However, those that failed between 2 to 4 years did worse. I'm not quite sure how to interpret it yet," said Dr. O'Donnell, adding that it suggests that the 2- to 4-year window "may be a critical time to intervene." **UT**

TimeLine for BCG / Interferon Bladder Instillations

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	6 Week Break
BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment	

Month 3	6 Week Break	Month 4-5	Month 4-5	Month 4-5	6 Week Break	Month 6
Cystoscopy		BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment		Cystoscopy

3 Month Break	Month 9	6 Week Break	Month 10-11	Month 10-11	Month 10-11	6 Week Break
	Cystoscopy		BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment	

Month 12	3 Month Break	Month 15	6 Week Break	Month 16-17	Month 16-17	Month 16-17
Cystoscopy		Cystoscopy		BCG / Interferon treatment	BCG / Interferon treatment	BCG / Interferon treatment

6 Week Break	Month 18	3 Month Break	Month 21	3 Month Break	Month 24	DONE!!!
	Cystoscopy		Cystoscopy		Cystoscopy	

Cystoscopies with cytologies continue twice per year for next 2 years (years 3-4) then annually thereafter as part of general surveillance program
Random bladder biopsies are recommended for the first (Month 3) cystoscopy and if negative are only repeated thereafter if either cystoscopy or cytology are clinically suspicious.

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INSTRUCTIONS: Before retiring for bed each night record your symptoms in each of the categories listed below using the following severity scale: 0= None, 1= Mild, 2= Moderate, 3= Severe.

SYMPTOM	Pre Treatment Day 0	Post Treatment Day 0	Post Treatment Day 1	Post Treatment Day 2	Post Treatment Day 3	Post Treatment Day 4	Post Treatment Day 5	Post Treatment Day 6
Burning on Urination	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Urgent Urination	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○
Bladder Pain/Spasm	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○
Flu-like Symptoms	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○
Joint Ache Arthritis	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○	○○○○
Frequency of Urination	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour	○>3 hours ○2-3 hours ○1-2 hours ○>1/hour
Blood in Urine	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots	○None seen ○Pink-red ○Red+clots ○Very Red Many clots
Fever	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F	○ None ○<100.5F ○<102.5F ○>102.5F

24855

46137

FORM TTE

Tolerance-Toxicity Evaluation

To Be Completed By Physician or Medical Staff ~ 1 Week After Each Treatment

PLACE BAR CODE ID HERE

Patient Identification

[ ][ ][ ] - [ ][ ][ ][ ] - [ ][ ][ ]

Initials *Last 4 SSN* *Site ID*

Date of Treatment

[ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Month *Day* *Year*

Medical Staff Verifier ID

[ ][ ][ ]

Initials

Treatment Cycle

- ○ Induction
- ○ Re-Induction
- ○ Maintenance Cycle A
- ○ Maintenance Cycle B
- ○ Maintenance Cycle C

Treatment Number

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

Induction or Re-Induction Only

How long did the patient retain the medication?

○ <1/2 hour ○ 1/2-1 hour ○ 1-1 1/2 hours ○ 1 1/2-2 hours ○ 2-3 hours ○ >3 hours

Treatment Toxicity Score

Please grade toxicity using the following scoring system:

0 = No symptoms
1 = Mild symptoms not requiring specific treatment
2 = Moderate symptoms requiring some treatment but no delay or dose reduction
3 = Moderate-Severe symptoms requiring treatment delay or dose reduction
4 = Severe symptoms requiring cessation of further therapy this treatment cycle
5 = Very severe symptoms requiring discontinuation of ANY further treatment

Category	Grade					
Cystitis	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
Hematuria	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
Flu-like Symptoms	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
Fever/Chills	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
Athritis/Arthalgias	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
Other(specify)	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5

[ ]

Record all specific treatments instituted to combat toxicity

○ None ○ Urinary analgesics ○ Tylenol/NSAIDs ○ Antispasmotics

○ Non-Quinilone antibiotics (ABs) ○ Quinilone ABs ○ TB-specific ABs

○ Steroids ○ Narcotics ○ Alpha blockers ○ Other

27042

FORM QOL

Quality of Life Survey

To Be Filled Out By Patient Before And After Each Course of Therapy

PLACE BAR CODE ID HERE

Patient Identification			Date			Medical Staff Verifier ID
___ -	____ -	___	__ /	__ /	____	___
Initials	*Last 4 SSN*	*Site ID*	*Month*	*Day*	*Year*	*Initials*

PLEASE RESPOND BASED ON YOUR FEELINGS OVER THE PAST FEW WEEKS

How satisfied were you with various aspects of your life?

	Very Satisfied	Somewhat Satisfied	Neutral	Somewhat Dissatisfied	Very Dissatisfied
Physical State	○	○	○	○	○
Mental State	○	○	○	○	○
Energy	○	○	○	○	○
General Health	○	○	○	○	○
Work Business/Domestic	○	○	○	○	○
Financial Situation	○	○	○	○	○
Leisure Activities	○	○	○	○	○
Independence in Daily Living	○	○	○	○	○
Everyday Life in General	○	○	○	○	○
Coping with Disease	○	○	○	○	○
General Abilities	○	○	○	○	○
Self-esteem	○	○	○	○	○
General Person	○	○	○	○	○
Everyday Life with Partner	○	○	○	○	○
Sexual Satisfaction	○	○	○	○	○
Family Life	○	○	○	○	○
Status in Family	○	○	○	○	○
Contact with Friends	○	○	○	○	○
Number of Friends	○	○	○	○	○
Contact with Others	○	○	○	○	○
Medical Treatment	○	○	○	○	○

How strongly did you feel:	Not at All	A Little	Somewhat	Much	A Great Deal
Affected by your complaints?	○	○	○	○	○
Your everyday life was affected by your health?	○	○	○	○	○
Your mood was affected by your health?	○	○	○	○	○
Dissatisfied with life in general on account of your health?	○	○	○	○	○

How would you estimate your general physical condition?

Very Poor ○1 ○2 ○3 ○4 ○5 ○6 ○7 Excellent

How would you estimate your quality of life in general?

Very Poor ○1 ○2 ○3 ○4 ○5 ○6 ○7 Excellent