BCG

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The importance of BCG Mainentance therapy: A large German retrospective analyses (2004) saw a "statistically significant superiority for BCG compared with MMC [Mitomycin intravesical chemo] for the prevention of tumor progression only if BCG maintenance therapy was provided."PubMed Abstract

Abstracts about the use of low dose bcg: RATIONALE: less side effects, better compliance with treatment protocols and just as effective:

Low dose BCG as adjuvant therapy for superficial bladder cancer and literature review

C. W. Cheng, M. T. Ng, S. Y. Chan, W. H. Sun ANZ Journal of Surgery Vol. 74 Issue 7 Page 569 July 2004:

Low dose BCG could be an alternative option of adjuvant therapy for superficial bladder cancer with acceptable toxicity and good compliance. PubMEd

Sufficient prophylactic efficacy with minor adverse effects by intravesical instillation of low-dose bacillus Calmette-Guerin for superficial bladder cancer recurrence.Int J Urol. 2003 Apr;10(4):183-9. Irie A, Uchida T, Yamashita H, Matsumoto K, Satoh T, Koh H, Shimura S, Iwamura M, Baba S.Department of Urology, Kitasato University School of Medicine Japan. "Conclusions: Half-dose of BCG Tokyo 172 strain had a similar efficacy and its toxicity was significantly lower compared to the standard dose. Thus, half-dose of this strain might be suitable, at least for initial BCG therapy, for the prophylaxis of bladder cancer recurrence. Further study would be necessary to clarify the efficacy of low-dose instillation in high-risk patients.

Medline Abstract

Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. J Urol. 2000 Jan;163(1):68-71;Losa A, Hurle R, Lembo A. Division of Urology, Ospedali Riuniti di Bergamo, Italy "Conclusions: Intravesical BCG is the best available conservative therapy for patients with carcinoma in situ of the bladder. Low dose BCG is similarly effective, with a lower incidence of side effects and long lasting positive outcome"

Medline Abstract

Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int. 2002 May;89(7):671-80. Hospital La Paz, Avenida San Luis 95, 28033 Madrid, Spain, Martinez-Pineiro JA, et al "Conclusions: We recommend continuing to use the standard dose for high-risk tumours, while we consider the reduced dose safe and effective for intermediate-risk lesions and for maintenance schedules"

Medline Abstract

The ablative effect of quarter dose bacillus Calmette-Guerin on a papillary marker lesion of the bladder.J Urol 2001 Feb;165(2):401-3 Mack D; Holtl W; Bassi P; Brausi M; Ferrari P; de Balincourt C; Sylvester R; European Organization for

Research and Treatment of Cancer Genitourinary Group

Source: "Conclusions: Quarter dose BCG has a clear ablative effect on superficial bladder cancer with a 61% response rate. Phase III trials are now required to compare its efficacy and toxicity to those of full dose BCG."

Medline abstract

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BCG is the most studied and most commonly prescribed immunotherapeutic agent for use in bladder cancer treatment. For more detailed BCG treatment information, see Dr. DL Lamms protocol, research and extensive list of referenced studies, including his findings about the efficacy of maintenance therapy.

A recent professional meeting slide presentation with transcript, Dec. 2002 click here; Dr. Lamm has a website as of 2005 where you can leave questions and get a second opinion: http://www.bcgoncology.com

On this page: treatment sex antibiotics pros, cons, other drug interactions BCG and PSA

risk of relapse after therapy further reading

New: BCG and use of statin drugs-the controversy

New 2007, can we predict response to BCG? Tools exist which may help

Bacillus Calmette-Guerin has been in use since the 1980's, and is the most proven and effective form of immunotherapy at this point in time. Immunotherapy has a mechanism of action different from that of chemotherapy. It uses materials made by your own body or made in a laboratory to boost, direct, or restore your body's natural defenses against disease.

Bacillus Calmette-Guerin (BCG), which is an inactivated form of the bacterium Mycobacterium tuberculosis, is given both intravesically mixed in a saline solution and instilled directly into the bladder via a catheter, as well as in the form of a percutaneous vaccine. Although it is not yet totally understood why BCG and other immunotherapies work against cancer, they are thought to elicit an immune response.

It's been shown that BCG induces a variety of cytokines into the urine of patients with non-muscle-invasive TCC, and that some cytokines have antiangiogenic activity. One study demonstrated that interferon- inducible protein 10 (IP-10) and its inducing antiangiogenic cytokines, interferon-gamma (IFN-gamma) and interleukin-12 (IL-12), are increased during intravesical BCG immunotherapy of bladder TCC. These data suggest that, in addition to a cellular immune response, BCG may induce a cytokine- mediated antiangiogenic environment that aids in inhibiting future tumor growth and progression.1

BCG has resulted in complete tumor regression in one half or more of treated patients with papillary tumors, and in more than 70% of those with CIS. Controlled studies have demmonstrated a significant reduction in tumor recurrence, protection from which has been observed to persist for 5 years or more. Dr. Lamm’s studies have also shown

statistically significant reductions in the rate of disease progression and a significant reduction in the mortality rate, after treatment with BCG immunotherapy.2

The proven effectivenes of BCG in treating carcinoma in situ has made it the treatment of choice for CIS.3 Although European studies have reported less spectacular results after a long term study of comparing BCG to Mitomycin C, the reported studies used a less than optimal protocol according to Dr. Lamm’s recommendations. Still, the superiority of BCG over chemotherapeutic agents in treating high risk tumors and CIS is acknowledged.4, 5

BCG is usually reserved for higher grade tumors or recurrences, while solitary, non-muscle-invasive papillary tumors are most often treated (if treated at all) with an intravesical chemo as first line of attack. Once a tumor has shown signs of muscle invasion (T2), BCG is no longer considered a viable option.

Though side effects vary with the individual, the great majority of people find BCG treatments tolerable with side effects being temporay, and some have no adverse reactions at all. Dysuria (pain or difficulty upon urination) and urinary frequency are expected as a consequence of the inflammatory response, and cystitis is the most frequent adverse reaction-occurring in up to 90% of cases. Blood in the urine may occur with cystitis and is seen in one-third of patients. Irritative bladder symptoms are unlikely in the week after the first intravesical BCG. Side effects of BCG are cumulatory, and generally increase with successive treatments.6 Some people complain of flu like symptoms including fatigue, joint pain and muscle ache. 7

Treatment

For maximum effect the solution should be instilled when the bladder is completely empty and remain in direct bladder contact for 2 hours. Patients are recommended to limit fluid intake for 8-12 hours, and to have no fluid intake for 4 hours before treatment is scheduled. Avoid direct skin contact during and after urinating as it may cause skin rash and irritation. You are advised to sit while urinating and to empty the bladder completely. Thorough cleansing of genital area and hands is advised.

The toilet must be neutralized of any live bacteria; this is done by pouring 2 cups of household bleach into the water and letting it stand for 15-20 minutes.

The bladder should be thoroughly flushed after BCG instillation by increasing fluid intake.

Call the doctor if you experience

- Urinary problems
  - continued pain and burning
  - urgency

frequency

blood or blood clots in the urine

Flu like symptoms

fever

chills

joint pain

Increased fatigue

Frequent or persistent coughing

Skin rash (despite having taken precautions mentioned above)

For a more complete description about use, side effects and possible complications, drug interaction, etc, see RxMed's Drug Reference for two commonly used strains of the vaccine: Pacis ImmuCyst . See also http://www.immucyst.com/ for more info.

It is not recommended to instill BCG until at least one-two weeks after resection of the tumor. BCG should not be given if irritative symptoms from the previous instillation are present, nor in the presence of undetermined fever or urinary tract infection. Fewer than one in 1000 people who use the BCG percutaneous vaccine develop significant local reactions, and potentially fatal disseminated disease develops in fewer than one in a million. Complications usually result from faulty technique, including the accidental intracutaneous injection of the stronger percutaneous vaccine, or poor selection of subjects for vaccination. BCG should never be given to people who are known to be infected with HIV. 8

The viability of BCG is crucial for induction of a local immune response and for effective therapy. Favorable results occur more frequently among patients who exhibit a granulomatous inflammatory response in the bladder and delayed hypersensitivity skin test response to purified protein derivative. Marked variability in viability of bacillus Calmette-Guerin organisms has been observed among different lots of BCG, and a direct relationship has been observed between vaccine viability and therapeutic efficacy. In one study, most patients who failed initial therapy with a low viability lot of bacillus Calmette-Guerin responded favorably to re-treatment with a higher viability lot.9

Sex

Men having this treatment can pass on BCG during sex. To protect your partner from coming into contact with BCG, you should not have sex for 48 hours after each treatment. Use a condom if you have sex at other times during the six weeks of treatment. You should also use a condom for sex for six weeks after treatment has ended.
http://www.accv.org.au/cancer1/patients/bladder/howtreated.htm

Drug interactions-Antibiotics

In case of BCG instillation therapy, the antibiotics in the class of quinolones, doxycycline and gentamycin should be avoided in concomitant urinary tract infections. In case of severe systemic complications, 5-quinolones might be used additionally if one of the anti-tuberculosis drugs including isoniazid, rifampicin or ethambutol is not tolerated. Cycloserine, previously proposed for the early treatment of BCG-sepsis is not recommended any more. Only the appropriate use of antibacterial drugs during intravesical BCG immunotherapy preserves the therapeutic safety and efficacy. X

Quinolone *antibiotics:

Trovan (trovafloxain mesylate), Trovan IV (alsatrofloxacin mesylate, Ciloxan (ciprofloxacin hydrochloride), Zagam (sparfloxacin), Elequin (levofloxacin), Levaquin (levofloxacin), Cipro* (ciprofloxacin), Maxaquin (lomefloxacin), Noroxin (norfloxacin), Floxin (ofloxin)

*Cipro is an often used antibiotic, though not always without side effects. For more info on Cipro you can look here: http://prostate.org/ciproeffects.html%20

Doxycyclines--Antibiotic/tetracyclines:

Periostat (Doxycycline Hyclate), Atridox (doxycycline hyclate), Vibramycin Ca (doxycycline calcium), Doryx (doxycycline hyclate), Doxycycline (doxycycline hyclate), Vibra Tabs (doxycycline hyclate), Monodox (doxycycline monohydrate)

gentamycin:

Garamycin (gentamicin sulfate), Genoptic (gentamicin sulfate ophth), Gentacidin (gentamicin sulfate ophth), Gentak (gentamicin sulfate ophth)

http://www.rxlist.com/

Antibiotics For bladder cancer

2006: A randomized controlled clinical trial of 115 patients determined the impact of the antibiotic Ofloxacin on side effects of BCG therapy; the findings were interesting, showing 22% fewer 'moderate' side effects, a lessing of severe complications between instillations 1 and 9 (54% vs. 76% respectively), and a better adherence to therapy, with 81% of the antibiotic group completing the therapy vs. 66% of those who received placebos. XX

Another line of research is investigating the usefulness of antibiotics against superificial bladder cancer, more on WebCafe, here

Other medicines:

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. When receiving BCG it is especially important that your health care professional know if you are taking any of the following:

Amphotericin B by injection (e.g., Fungizone) or

Antineoplastics (cancer medicine) or

Antithyroid agents (medicine for overactive thyroid) or

Azathioprine (e.g., Imuran) or

Chlorambucil (e.g., Leukeran) or

Chloramphenicol (e.g., Chloromycetin) or

Colchicine or

Corticosteroids (cortisone-like medicine) or

Cyclophosphamide (e.g., Cytoxan) or

Cyclosporine (e.g., Sandimmune) or

Flucytosine (e.g., Ancobon) or

Ganciclovir (e.g., Cytovene) or

Interferon (e.g., Intron A, Roferon-A) or

Mercaptopurine (e.g., Purinethol) or

Methotrexate (e.g., Mexate) or

Muromonab-CD3 (e.g., Orthoclone OKT3) or

Plicamycin (e.g., Mithracin) or

Zidovudine (e.g., AZT, Retrovir)

Because these medicines reduce the body's natural immunity, they may prevent BCG from stimulating the immune system and will cause it to be less effective. In addition, the risk of infection may be increased.

Other medical problems

The presence of other medical problems may affect the use of BCG. Make sure you tell your doctor if you have any other medical problems, especially:

Fever—Infection may be present and could cause problems

Immunity problems—BCG treatment is less effective and there is a risk of infection

Urinary tract infection—Infection and irritation of the bladder may occur

Concerns over high grade tumors - long term risk

Patients with high-risk non-muscle-invasive bladder tumors who retain their bladders owing to successful local BCG therapy have an increased risk of developing extravesical (outside the bladder) urothelial tumors.

One 2002 study involving 307 patients with mulitiple, recurrent Ta, T1 and CIS tumors were followed for a median of 12 years (range, 10--18 years). Extravesical tumors were detected during follow-up of positive urine cytology after no tumor was found in the bladder. Of the 307 patients, 78 (25%) developed tumors in the upper urinary tract (UTT). Of the 251 men 61 (24%) had tumors detected in the prostatic urethra or ducts (T4p). The median time to UTT and T4p was 56 and 11 months, respectively. UTT and T4p were diagnosed more frequently during the first 5 years, but such tumors occurred over 15 years of follow-up. The median time to UTT was 50 months among 246 patients with tumor recurrence in the bladder vs 114 months in 61 patients with no bladder recurrences. 88% of UTT occurred in patients with intact bladders and 12% after cystectomy. 32% of UTT and 44% of T4p relapses were lethal. 12

2005: Risk of understaging upon progression after BCG fails in high-risk non-muscle-invasive blc: "Five-year disease-specific survival rate was significantly lower in understaged (38%) as compared with not-understaged patients (90%) after a median follow-up of 40-months (range 1-142) (p=0.006). Overall five-year disease-specific survival was 79%. CONCLUSIONS: RC should be performed prior to progression in high risk non-muscle-invasive tumors that fail after TUR and BCG. In patients with clinical and pathological nonmuscle invasive disease,radical cystectomy (RC) provides an excellent disease-free survival. One third of patients with high-risk non-muscle-invasive bladder tumors who underwent RC after BCG failure were understaged and had a shorter survival. Tumor in the prostatic urethra at endoscopic staging was the only factor associated to understaging and shorter survival.14

BCG and PSA

A study published in the November 2000 issue of the Journal of Urology showed that used of BCG can raise PSA (prostate specific antigen), and that intravesical BCG therapy is associated with significantly elevated PSA in up to 40% of cases. The authors state: "This effect is self-limited and PSA reverts to normal in 3 months. Therefore, we suggest that prostate biopsy be withheld in such patients and PSA monitored." 13 2003: "Endovesical BCG administration produces an increase on serum PSA levels. This variation is higher in patients with history of TURP." 15

Studies and trials are underway for other intravesical immunotherapeutic agents such as interferon alpha2b (or Intron A), which has shown activity against papillary tumors and CIS both as primary treatment and as secondary treatment after failure of other intravesical agents. 11 See below.

BCG and Statin drugs in the news - is there a risk?

Hyperlipidemia, lipid and lipoprotein abnormalities are very common in the bladder cancer community and general population; hyperlipidemia is regarded as a highly treatable risk factor for cardiovascular disease from high cholesterol-caused artherosclerosis. Statin drugs are commonly used for this purpose and considered so safe they available over the counter in many countries.

An article published in Dec.'06's New England Journal of Medicine 16 by Hoffman and colleagues reported that statins posed a risk for bladder cancer disease progression when used during BCG treatments, and advised stopping statin use during BCG therapy. However, those findings were quickly refuted in March, '07, in another article in the New England Journal of Medicine, from Dr. A. Kamat 17, expert uro-oncologist from M.D. Anderson's cancer center, who has also investigated the use of statins concomitant with BCG therapy, in a larger patient cohort, and for a longer period of time. That article states;

"..There was no difference in outcomes, even when accounting for whether patients received only induction BCG therapy or induction BCG plus maintenance therapy." In a review on UroToday.com, Dr Kamat states: "At the current time, treating urologists and patients should view the available data as inconclusive, at best. This is especially important since patients with bladder cancer commonly use statins, and some reports have documented antiproliferative effects of statins

urothelial cancer cell lines. Further more, since it has been shown that discontinuation of statin therapy can have adverse cadiac outcomes, it seems prudent to continue statin therapy in bladder cancer patients who are on BCG, until more robust data to suggest otherwise are presented. " [Review; Urotoday, April 2007]

Can we predict non-response? Researchers reported in 2007 that heat shock proteins (HSPs) could be useful predictive markers in BCG responses. A significant correlation was found between lack of expression of HSP90 and BCG response. HSP expression was evaluated by immunochemistry. Low HSP90 expression (<40%) could be useful to predict BCG failure and early stage cystectomy could be proposed for these selected patients with primary high-risk grade 3 non-muscle-invasive bladder tumours.

Full text article: HSP90 Expression: A New Predictive Factor for BCG Response in Stage Ta-T1 Grade 3 Bladder Tumours Thierry Lebreta, b, , , R. William G. Watsonb, Vincent Moliniéa, Jean-Eudes Poulaina, Amanda O’Neillb, John M. Fitzpatrickb and Henry Bottoa aDepartment of Urology and Pathology, Hôpital Foch, Suresnes, France bSchool of Medicine and Medical Science, Mater Misericordiae University Hospital, and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland European Urology

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For a short history of how the BCG vaccine was developed, read this abstract from an article published in Sept. '99 issue of Toxicon; Doctor Albert Calmette 1863-1933: founder of antivenomous serotherapy and of antituberculous BCG vaccination, By BJ Hagwood.

Further Reading:

Oct. 2004: BCG Immunotherapy: Bladder Cancer and Beyond: a panel of experts exchange state of the art information:

http://www.immucyst.com/files/bcg_16final_908.pdf

For a great article which explains in depth the mechanisms of action, research on the efficacy of, and latest discoveries in the field of intravesical therapy (including both chemo and immunotherapeutic agents), register (it's free and open to the public) at http://www.medscape.com and see (from The Journal Room: 'Infections in Urology') : Intravesical Therapy for Superficial Bladder Cancer Ashish M. Kamat, MD, Donald L. Lamm, MD West Virginia School of Medicine, Morgantown, W. Va. March, 1999

For some very interesting articles and discussions between experts around the world, see this issue of European Urology,"BCG - A New Standard for Superficial Bladder Cancer", online here: http://www.immucyst.com/21-S2-92.html

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