Current Recommendations for BCG Immunotherapy

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Patient Selection

Patients with a solitary papillary tumor that appears to be low grade can be
best treated with single instillation of chemotherapy (Thiotepa 30mg/30cc water
for 30 minutes, for example) at the conclusion of the resection. Single instillations
have been demonstrated to be effective with Thiotepa, Adriamycin (50mg/50cc),
Mitomycin (20mg/20cc), and Epirubicin, even in these "low risk" patients.
No significant advantage of continued treatment has been demonstrated in controlled
studies, but continued treatment (4-6 week) is appropriate for CIS or incomplete
resection. BCG is not necessary unless tumor recurrence becomes a problem for
these patients. Patients with CIS, Grade 3 TCC, or lamina propria invasion are
best treated with BCG. BCG has been proven to be superior to chemotherapy (Thiotepa,
Adriamycin, Mitomycin, and Epirubicin) in comparative controlled studies and
BCG, but not chemotherapy, is found to significantly reduce disease progression.

Preparation and Administration

Two BCG preparations are commercially available in the US: Connaught (TheraCys)
and Tice (Organon) BCG. Both are highly effective and safe, when used carefully.
In my study comparing Connaught BCG vs doxorubicin (New Engl J Med 25:1205,
1991) using 6 week induction and single maintenance instillations every 3 months
for two years, complete response was seen in 70% of patients with CIS vs 34%
with doxorubicin, and 48% vs 18% of patients remained disease free 5 years.
In my comparison TICE BCG using a monthly maintenance schedule with mitomycin
C, 55% had complete response vs 44% CR with mitomycin (Urol. Oncol. 1:119, 1995).
In my comparison of 6 week induction BCG (Connaught) vs three-week maintenance,
complete response was increased from 68% to 84%. I therefore recommend the three
week maintenance schedule (see below).

Both of the Connaught BCG studies used percutaneous BCG. My randomized comparison
of intravesical with or without percutaneous TICE BCG administration (J Urol
145:738, 1991) showed no added benefit of percutaneous BCG. However, more than
90% of healthy adults will convert to a positive PPD skin test with percutaneous
BCG, and a positive PPD increases the complete response in CIS from 49% to 77%
(P<0.0001). Therefore, our next study will use percutaneous BCG. A single
percutaneous treatment at the start of treatment should suffice. One drop of
the BCG suspension to be given intravesically can be placed on the cleansed
inner thigh and the skin punctured four times with a 28g needle (Tine technique).
Intravesical BCG should not be given within one week of bladder tumor resection.
About two weeks after resection 81mg of Connaught BCG (TheraCys) or 50mg of
TICE BCG in 50cc sterile normal saline can be instilled via a small catheter.
I have patients lie on their abdomen for 15 minutes in the office to displace
the anterior bubble that enters the bladder as the air is displaced from the
catheter. Thereafter they leave the office and are asked to retain the suspension,
if possible, for two hours. Treatments are continued weekly to a total of 6
instillations. Patients may be given Pyridium for dysuria, anticholinergics
for frequency, and/or acetaminophen for pain. We expect to have mild to moderate
irritative symptoms beginning after the second or third instillation. Symptoms
should last no more than 2 days. If symptoms are more severe or prolonged, isoniazid
300mg daily can be used to treat the symptoms. If symptoms respond within one
week, isoniazid can be discontinued after the second or third week. If symptoms
do not respond or evidence of BCG infection other than local cystitis is present,
we treat with isoniazid 300mg plus rifampin 600mg daily for three months (see

Antitubercular antibiotics are infrequently necessary. When patients begin to have increased symptoms following BCG instillation, the dose can be reduced to 1/3, 1/10, or 1/100th as needed to prevent significant side effects with subsequent treatment. Never give BCG if symptoms from previous BCG administrations are still present, and never instill BCG if the catheterization is traumatic or bloody. Nothing is lost by postponing BCG treatment if patients have symptoms, because symptoms are evidence of continued immune stimulation. Excess BCG administration is associated with increased side effects and suppression of antitumor immune response.

There is no need to repeat cystoscopy until at least 4-6 weeks after completion of the 6-week induction course. Unlike cytotoxic chemotherapy, which kills cells by direct contact, BCG kills cells by inducing an immune response. It takes 6 weeks for the optimal immune response to develop in most patients when given the initial course of BCG. It then takes a period of time, as long as 6 months in some patients, for this immune response to destroy all remaining tumor cells. In my SWOG study of three week maintenance BCG, 14% of patients who had residual CIS at the three month evaluation went on to have complete response by the six month evaluation without further treatment. With three additional BCG instillations at 3 months, the complete response per cent increased by 30% at 6 months. Therefore, the most important time for evaluation in BCG treated patients is at 6 months.

Carcinoma in situ and Grade 3 TCC

Patients with CIS or Grade 3 TCC are at long-term risk for tumor recurrence in the bladder, lower ureters, and prostatic urethra. In Herr's experience with BCG treatment without maintenance therapy, 69% had tumor recurrence or progression by ten years (JCO. 16:1099,1998). Of 307 patients, 25% developed upper tract tumor (median 56 months) and 32% of relapses were fatal. Of 251 men, 24% developed TCC of the prostatic urethra (median 11 months), and 44% or these relapses were fatal. Therefore, I recommend annual cystoscopic examination under anesthesia, with upper tract washes and retrogrades (followed by ureteroscopy if the retrograde shows anything) in these patients. The prostatic urethra should be biopsied. In patients with diffuse or aggressive disease, consideration should be given to resection of the ureteral orifices to induce reflux. After confirming reflux with a cystogram, intravesical BCG can then be used to treat the lower ureters. Consideration should also be given to transurethral resection of the prostate in these patients to reduce the risk of occult TCC in the prostatic ducts progressing to invasive disease. TUR will also increase the contact of BCG with the prostatic urethra.

Maintenance BCG

Intravesical chemotherapy reduces short-term (2 year) tumor recurrence by 20% or less when compared to surgery alone. Long-term (5-8 year) recurrence is reduced by 7% (Pawinsky A , EORTC/MRC: J Urol. 156:1934-41,1996), but unfortunately chemotherapy does not reduce stage progression. Though not statistically significant, in both our review and the EORTC/MRC meta analysis progression was actually higher in patients treated with chemotherapy than in controls. BCG immunotherapy using 6 week induction, monthly maintenance for one year, single quarterly maintenance for two years, repeat 6 week instillation, or even 6 week instillations for 2 years reduces tumor recurrence by about 40% short-term and 20% long-term. Several studies have shown that BCG does reduce tumor progression as well. Previous randomized controlled trials have shown no advantage to maintenance BCG, but my maintenance schedule using 3 weekly treatments has been found to be dramatically superior. In our SWOG study 660 patients received induction BCG and 550 were randomized to observation vs maintenance BCG. At the three month evaluation, 192 in each arm were disease free and therefore eligible for
evaluation of the benefit of maintenance BCG. This study was closed to accrual in 1987, so follow-up now exceeds 12 years. The results of induction BCG were excellent, and very similar to our experience and that of others with BCG immunotherapy: only 52% of patients developed tumor recurrence. Based on previous reports, one would expect that 70% or more of patients treated with chemotherapy and 77% of patients treated with surgery alone would have had recurrence. In patients who received maintenance BCG, only 25% had recurrence, or 27% fewer than induction BCG (P<0.000001, and 45% and 52% fewer than expected with chemotherapy or surgery alone). Progression was further significantly reduced (Lamm, J. Urol. 157:4, (831), 1997 and when all randomized patients are included, mortality is also significantly reduced (Lamm, J Urol 143:341(610), 1990). Simply stated, BCG reduces long-term recurrence by 20% compared to chemotherapy, and maintenance BCG reduces long-term recurrence by 25% relative to standard BCG. BCG reduces disease progression compared with surgery or surgery plus chemotherapy, and maintenance BCG results in a further significant reduction in progression.

Technique of BCG Maintenance

Following the standard 6 week induction course of BCG, patients have cystoscopy at three months. In patients with no disease or recurrence of disease without progression, three weekly instillations of BCG are given one week after cystoscopy. Following the six month cystoscopy, an additional three weekly instillations are given. The three week course of BCG is then repeated at 12, 18, 24, 30, and 36 months. In the SWOG study the rate of tumor recurrence increased one year after completion of maintenance therapy. In patients with CIS, Grade 3, or stage T1 disease I therefore recommend continuation of three week maintenance at years 4, 5, 6, 8, 10, and 12. If patients have moderate to severe side effects with the first or second of the three maintenance instillations, the remaining instillations in that course should be deleted. At the next treatment interval (eg 6 months later), instillations should be initiated with log-lower BCG dose, 1/3, 1/10, or even 1/100th CFU BCG in 50cc preservative-free saline. If patients have no symptoms from BCG instillation, or if they have tumor recurrence, consider doing a PPD skin test. Percutaneous BCG may need to be repeated if the skin test is negative (less than 5mm of induration).

Upper Tract Transitional Cell Carcinoma

Intravesical therapy does not eradicate TCC of the distal ureters, and upper tract TCC is most likely to occur in patients with CIS of the bladder. Solsona et al reported TCC in the distal ureter in 25% of 138 patients with CIS treated with cystectomy compared with 2.3% of 786 patients with superficial bladder cancer and 2.9% of 179 patients with invasive disease (Solsona, 1997). In patients with CIS treated with BCG, the incidence of TCC in the upper ureter is likely to be higher than the 25% reported by Herr in his combined series that included patients without CIS.

CIS of the lower ureters can be managed by resection of the anterior wall of the intramural ureter over an indwelling stent to induce reflux. After confirming reflux with a cystogram, the lower ureters can be treated with intravesical BCG. Most of these patients will have had an induction course of BCG, so three rather than six instillations would be appropriate. An additional three weekly instillations can be given at three months, and followed with maintenance at 6 month intervals.

For patients with renal pelvic or upper ureteral TCC who are not candidates for nephroureterectomy, BCG can be given through a percutaneous nephrostomy tube. To decrease the chance of pyelovenous backflow, a manometer is used in...
a manner analogous to Renacidin irrigation. These patients can be safely treated
in the office. The same dose of BCG is given in 50cc of saline and infused over
2 hours. I generally give a "6 plus 3" course, confirm response with
cytology and a nephrostogram, and then pull the nephrostomy tube. Alternatively,
BCG can be given via ureteral catheters or intravesically, if reflux to the
tumor site is confirmed.

TCC of the Prostatic Urethra

Recurrence of TCC in the prostatic urethra is common, and in patients with
CIS or high grade TCC must be carefully sought. Intravesical BCG can eradicate
TCC in the prostatic urethra. Shellhammer reported 70% CR without TUR, but I
prefer to resect the prostate to stage the disease and, hopefully, improve direct
contact with BCG. I begin with a superficial, circumferential resection of the
prostatic urethra. This specimen is collected and sent separately to pathology.
I then do a second circumferential resection and send this specimen as "margin."
The results of BCG immunotherapy are excellent if there is no invasive TCC in
the margin.

Treatment of BCG Side Effects and Complications

By lowering the dose of BCG to 1/3, 1/10/, 1/30, or 1/100th as needed to avoid
increased irritative or systemic symptoms, very few patients have any difficulty
with BCG immunotherapy. If irritative symptoms persist beyond three days, fail
to respond to symptomatic treatment, or are severe isoniazid 300mg a day can
be given. If patients respond promptly, I generally stop treatment after only
one or two weeks. In patients who have true BCG infection requiring antituberculous
antibiotics, for example symptomatric prostatitis, epididymitis, or hepatitis,
isoniazid plus rifampin 600mg daily should be given for 3-6 months. With serious
infections triple antibiotic therapy may be needed, and ethambutol 1200mg daily
or a fluoroquinolone may be added. BCG is relatively resistant to cycloserine
and pyrazinamide.

BCG sepsis can be fatal, and prompt and effective treatment is necessary. Since
cultures are often negative, treatment must be given empirically. Patients require
coverage for gram negative sepsis as well until blood cultures are negative.
With sepsis the current treatment of choice is no longer cycloserine, but isoniazid,
rifampin, and prednisone 40mg daily. Caution must be taken to taper the prednisone
slowly because hypotension may return when prednisone is stopped. Occasionally
higher doses of prednisone are required. Though a major component of this reaction
is hypersensitivity, prednisone alone without isoniazid and rifampin should
not be given. In our animal model, prednisone alone increased mortality, but
prednisone plus antibiotics markedly improved survival when compared with antibiotics
alone.

Additional and Alternative Treatment

Our double blind comparison of recommended daily allowance vitamins versus high
doses of vitamins A, C, B6, E, and zinc (Lamm, 1994) in BCG treated patients
demonstrated a remarkable and highly significant 40% further reduction in tumor
recurrence. We now recommend supplemental vitamins for bladder cancer patients.
The preparation we now use has been modified (improved, we hope) from our original
study based on subsequent research. The preparation, called "Oncovite,"
is made by Mission Pharmacal. The dose is two tablets twice a day (only three
da day for persons under 100 lb). It is available over the counter, but generally
has to be ordered by the pharmacy (800-531-3333).

If disease progression occurs, or grade 3 disease is present after 6 months
of BCG treatment, cystectomy is generally recommended. For less aggressive recurrent
disease, the chemotherapy options remain. Valstar (800 mg) has been recently
approved for CIS patients who fail BCG and are not candidates for cystectomy.
Eighteen percent or more of patients will have complete response. Interferon
has a 47% complete response rate in CIS, and we have seen long term responses
and responses after BCG failure (Glashan). We have had a favorable experience
with KLH (48% CR, Lamm,1996), and have an ongoing clinical trial. Photodynamic

therapy can also be very effective in BCG failures (Nseyo).

BCG Treatment Schedule:

***GRAPH***

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* Bladder and prostatic urethra biopsy and ureteral wash for G3 or CIS

Simplified summary below

MAINTENANCE BCG IMMUNOTHERAPY: EVIDENCE OF ADDITIONAL PROTECTION AGAINST

CANCER. A SOUTHWEST ONCOLOGY GROUP STUDY. DL Lamm, BA Blumenstein, JD

Crisman, JE Montie, BA Lowe, MF Sarosdy, RD Bohl, HB Grossman, TM Beck,

JT Leimert, ED Crawford, U Kosecka, and R Wittes

On May 5, 1999, Donald Lamm, MD, discussed a study recently completed by the
Soutwest Oncology Group (SWOG) at the American Urological Association meeting
in Dallas. Dr. Lamm reported that three-week maintenance therapy with BCG vaccine (Calmette-Guerin bacillus) in 385 subjects increased complete response in pre-invasive bladder cancer from 70 percent to 84 percent and reduced recurrence from 52 percent to 25 percent at eight years. The maintenance schedule also significantly reduced disease progression. BCG maintenance therapy also reduced the incidence of other cancers, primarily prostate cancer.

Introduction: Three-week maintenance BCG, when compared to standard 6-week induction, increases complete response in CIS from 70% to 84%, reduces recurrence of Ta, T1 TCC from 52% to 25% at 8 years, and significantly reduces disease progression/worsening. The increased toxicity of maintenance BCG has been noted, but other benefits have been largely ignored. METHODS: To test the hypothesis that maintenance BCG immunotherapy might protect against the development of other malignancies as well as reduce bladder tumor recurrence, the incidence of other malignancies in patients enrolled in SWOG 8507 was recorded.

RESULTS: Seventy of the 35 randomized, evaluable patients developed malignancy other than TCC during the 8 year follow-up: 46/202 (23%) in the induction-only arm and 24/183 (13%) in the maintenance arm (relative risk 0.68, P=0.014). The local immune response is considered to be of primary importance in BCG immunotherapy, and up to 75% of men develop granuloma in the prostate following intravesical BCG. Notably, the reduction in the incidence of prostate cancer was greater than the reduction in other malignancies: 14 of 179 men (6.9%) in the induction arm versus 5 of 151 (3.3%) in the maintenance arm. Only one of these five had advanced stage carcinoma of the prostate (Stage C) compared with six (43%, 3 stage C, 3 stage D) patients in the induction arm (RR 0.4, P=0.04). CONCLUSION: Stimulation of the immune system with 3-week maintenance BCG appears to reduce the incidence of subsequent malignancy, particularly carcinoma of the prostate. Immune stimulation may reduce the risk of cancer associated with age-related waning of immunity.

For the latest published findings on maintenance therapy, see abstract below references.

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MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

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ABSTRACT

Purpose: Bacillus Calmette-Guerin (BCG) immunotherapy has been widely accepted as the optimal treatment for carcinoma in situ and high grade superficial transitional cell carcinoma. However, controversy remains regarding the role of maintenance therapy, and its long-term effect on recurrence and progression.

Materials and Methods: All patients in the study had transitional cell carcinoma of the bladder with carcinoma in situ or an increased risk of recurrence. The criteria for increased risk were 2 or more episodes of tumor within the most recent year, or 3 or more tumors within 6 months. At least 1 week following biopsy of carcinoma in situ and resection of any stage Ta or T1 transitional cell tumors 660 patients were started on a 6-week induction course of intravesical and percutaneous Connaught BCG. Three months following initiation of BCG induction therapy 550 consenting patients were stratified by purified protein derivative skin test and the presence of carcinoma in situ, and then randomized by central computer to receive BCG maintenance therapy (maintenance arm) or no BCG maintenance therapy (no maintenance arm). Maintenance therapy consisted of intravesical and percutaneous BCG each week for 3 weeks given 3, 6, 12, 18, 24, 30 and 36 months from initiation of induction therapy. The 384 eligible patients who were disease-free at randomization constitute the primary intent to treat analytic group because they could be followed for disease recurrence. All patients were followed for adverse effects of treatment, recurrence, disease worsening and survival.

Results: No toxicities above grade 3 were noted in the 243 maintenance arm patients. The policy of withholding maintenance BCG from patients with increased side effects may have diminished the opportunity to observe severe toxicity. Estimated median recurrence-free survival was 35.7 months (95% confidence interval 25.1 to 56.8) in the no maintenance and 76.8 months (64.3 to 93.2) in the maintenance arm (log rank p <0.0001). Estimated median time for worsening-free survival, defined as no evidence of progression including pathological stage T2 disease or greater, or the use of cystectomy, systemic chemotherapy or radiation therapy, was 111.5 months in the no maintenance and not estimable in the maintenance arm (log rank p = 0.04). Overall 5-year survival was 78% in the no maintenance compared to 83% in the maintenance arm.

Conclusions: Compared to standard induction therapy maintenance BCG immunotherapy was beneficial in patients with carcinoma in situ and select patients with Ta, T1 bladder cancer. Median recurrence-free survival time was twice as long in the 3-week maintenance arm compared to the no maintenance arm, and patients had significantly longer worsening-free survival.

Summary:

1. Induction round of six weekly instillations. (Month 0)

2. Wait three months and have cystoscope.
3. If all clear, wait a week and begin first maintenance round of 3 weekly instillations (Month 3)
4. Wait three months and have cystoscope.
5. If all clear, wait a week and begin second maintenance round of 3 weekly instillations (Month 6)
6. Wait three months and have cystoscope.
7. Wait three months and have cystoscope.
8. If all clear, wait a week and begin third maintenance round of 3 weekly instillations (Month 12, or Year 1)
9. Wait three months and have cystoscope.
10. Wait three months and have cystoscope.
11. If all clear, wait a week and begin fourth maintenance round of 3 weekly instillations (Month 18)
12. Wait three months and have cystoscope.
13. Wait three months and have cystoscope.
14. If all clear, wait a week and begin fifth maintenance round of 3 weekly instillations (Month 24, or Year 2)
15. Wait three months and have cystoscope.
16. Wait three months and have cystoscope.
17. If all clear, wait a week and begin sixth maintenance round of 3 weekly instillations (Month 30)
18. Wait three months and have cystoscope.
19. Wait three months and have cystoscope.
20. If all clear, wait a week and begin seventh maintenance round of 3 weekly instillations (Month 36, or Year 3)
21. If all remains clear, continue with maintenance rounds of 3 weekly instillations at years 4, 5, 6, 8, and 10.

Thanks to Crilly Butler for the above summary

back to superficial bladder cancer
back to immunotherapy
back to dr. lamm's protocol