The right choice for treatment or prophylaxis of superficial bladder cancer

- Highly effective
- Fewer recurrences
- Long term benefits
- Well-tolerated
- Safe, easy to handle
- Dose flexibility

Immunotherapy that works
Highly effective

BCG Culture SSI (Danish strain 1331) is significantly superior to mitomycin C for superficial bladder cancer in patients at high risk for progression and recurrence of their disease.

A large Nordic randomised clinical trial demonstrated a substantially lower recurrence rate, a longer time to treatment failure, and fewer cystectomies for patients treated with BCG Culture SSI.

Response to Immunotherapy with BCG Culture SSI in High Risk Patients:

<table>
<thead>
<tr>
<th></th>
<th>BCG Culture SSI</th>
<th>Mitomycin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>49%</td>
<td>34%</td>
</tr>
<tr>
<td>Disease-free - TA/T1</td>
<td>48%</td>
<td>35%</td>
</tr>
<tr>
<td>Disease-free - CIS</td>
<td>54%</td>
<td>33%</td>
</tr>
<tr>
<td>Crossover treatment*</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>Cystectomies</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

* Second-line treatment after initial treatment failure

Response to therapy with BCG Danish strain 1331

<table>
<thead>
<tr>
<th></th>
<th>BCG Control p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>50 45</td>
</tr>
<tr>
<td>Patients with recurrence</td>
<td>24 38</td>
</tr>
<tr>
<td>Relative risk of recurrence</td>
<td>0.62 1.63</td>
</tr>
<tr>
<td>Recurrence rate / year</td>
<td>0.49 1.11</td>
</tr>
<tr>
<td>Recurrence rate /100 patients: months</td>
<td>4.0 9.25</td>
</tr>
<tr>
<td>Mean interval to first recurrence (months)</td>
<td>17.6 10.9</td>
</tr>
<tr>
<td>Mean recurrence interval (months)</td>
<td>24.7 10.8</td>
</tr>
<tr>
<td>Stage progression (No. of patients)</td>
<td>6 10</td>
</tr>
</tbody>
</table>

Response to therapy with BCG Danish strain 1331 after TUR in a patient population at very high risk for tumor recurrence and progression showed a definite advantage for patients in the BCG group compared to those receiving only TUR.

“BCG was superior regarding recurrence prophylaxis, since patients given BCG had fewer recurrences and a significantly longer time to treatment failure compared to those given mitomycin C.”

“When the results of initial and crossover treatment were combined, that is complete responses after initial and crossover therapy, 131 of 250 evaluable cases (52%) were disease-free (80 given BCG and 51 given mitomycin C).”

“Prior treatment with intravesical chemotherapy does not exclude excellent response to intravesical BCG therapy.”

“IT should be reasonable to state that intravesical BCG following complete transurethral resection rather than cystectomy is presently the treatment of choice for stage T1 disease.”

“...Excellent results...”

Comments on the use of BCG Danish strain 1331

DL Lamm: “The observation that BCG is highly effective in primary and recurrent tumors, stage T1 tumors and particularly high grade tumors is noteworthy.”

MJ Droller: “...Excellent results...”
Long-term benefits

Patients at high risk for recurrence or progression of superficial bladder cancer can expect to obtain an extended disease-free period after therapy with BCG Culture SSI \(^4,6,8,9\) even after prior failure with chemotherapy \(^4,7\).

<table>
<thead>
<tr>
<th>BCG Culture SSI (months)</th>
<th>Ta/T1</th>
<th>Dysplasia/CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.9</td>
<td>not attained</td>
<td></td>
</tr>
<tr>
<td>MMC (months)</td>
<td>14.9</td>
<td>16.9</td>
</tr>
</tbody>
</table>

"(A) significant percentage of patients stage T1 tumors can be effectively controlled with intravesical BCG for prolonged periods."

Well-tolerated

The great majority of patients experience only mild-to-moderate side effects of short duration, which are believed to be the result of a positive immune response to BCG Culture SSI. Serious adverse events occur in less than 3% of the patients treated with BCG Culture SSI \(^4,6,8,9\).

Safe, easy to handle

The safety of the treatment is enhanced by the stability of BCG Culture SSI, ensuring a constant and reliable range of CFUs in each dose.

BCG Culture SSI is produced in vials which gives added security to the health professional by allowing a safe and convenient closed system of reconstitution.

Dose flexibility

For certain patients, lower doses of BCG, especially for maintenance therapy, may be desirable \(^3,10\). Presentation of BCG Culture SSI in vials of 30 mg allows the urologist the option of choosing a lower dose of BCG Culture SSI for selected patients.

"The side effects of BCG therapy were mild, brief and easily controlled with conservative measures."

BCG Culture SSI therapy significantly improves the prognosis for high-risk patients with CIS or dysplasia \(^4,9\).

80% of patients with primary CIS experienced a long-term effect after treatment with BCG Culture SSI \(^9\).

A lasting complete response of 58% was seen in patients with T1G3 disease who received BCG Culture SSI \(^7\).

Therapy with BCG Culture SSI has been shown to induce a positive, long-acting immune response in the bladder \(^1\), believed to be necessary for long-term clinical effect \(^1\).
Aseptic insertion of a urethral catheter must be performed and the catheter is removed, and the patient is instructed to retain the suspension in the bladder for 2 hours, if possible. Restriction of fluid intake 3-6 hours prior to instillation may be recommended for patients with a limited bladder capacity. As BCG Culture SSSI is not a biodegradable material, the suspension may be voided in a normal manner, and no special precautions are necessary.

Adverse Reactions

Mild-to-moderate transient reactions: The reactions described below are generally mild-to-moderate, normally lasting no longer than 2 days, and are believed to be the result of a positive immune response to BCG. Local side effects, such as dysuria, increased urinary frequency, cystitis and hematuria are common. Mild systemic reactions such as fever or chills occur in a significant number of cases, and malaise or myalgia may also occur. Antipyretics, liquids and/or mild analgesics may be used to manage these symptoms. Moderate side effects may also be treated prophylactically with a single dose of 300 mg daily for 3 days, at each instillation.

Uncommon and seldom side effects: The complications listed in this section are seldom seen, occurring most often after 3 or more instillations, or in connection with a maintenance regimen. Fever over 39°C, which does not disappear within 24-48 hours after the patient receives liquids and antipyretics, and/or a period with malaise and fever, during which the symptoms increase, can indicate a systemic infection. BCG immunotherapy should be discontinued until a systemic infection has been ruled out. Immunotherapy may be reinitiated with caution if necessary.

Allergic reactions, such as arthralgia, myalgia or rash, occur in a very few patients. Macroscopic hematuria, bladder contraction or temporary urethral obstructions are also rare complications. Localised BCG infections, such as prostatitis or epididymo-orchitis, or systemic reactions (including hepatitis or pneumonia) are extremely rare, but necessitate immediate cessation of immunotherapy and referral to an infectious disease specialist for treatment with antituberculous therapy. A systemic BCG infection can be a life-threatening complication. It is recommended to institute immediate triple antituberculous treatment together with Prednisone 50-100 mg daily or Ciclesonine 500 mg, twice daily.

Storage

The resuspended solution may be kept for up to four hours, protected from light. Freeze-dried BCG Culture SSSI should be stored and transported continuously at -2º - +8º C. BCG Culture SSSI deteriorates when exposed even for short periods to direct sunlight and diffuse daylight (also indoors). During storage in a refrigerator (between +2º - +8º C) the product is stable until indicated date of expiration.

Information

Please refer to prescribing information for full details.

Information

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Ordering

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References:

BRIEF PRESCRIBING INFORMATION

Description

BCG Culture SSSI for immunotherapy is a freeze-dried preparation of attenuated Mycobacterium bovis (BCG), Danish strain 1331.

This product should only be prescribed and used by doctors with special knowledge of cancerous diseases and their treatment.

Composition

1 vial of freeze-dried BCG Culture SSSI contains:

- 30 mg Mycobacterium bovis (BCG) Danish strain 1331,
- approximately 2.5x10³ CFU,
- 40 mg sodium glutamate,
- 1 dose = 4 vials

Indications

This product is intended for instillation in the urinary tract after transurethral resection, as immunotherapy against primary or recurrent bladder cancer, and maintenance therapy. Immunotherapy with BCG Culture SSSI should be administered in the form of intravesical instillations or local application, or in combination with other local treatment modalities. Immunosuppressive treatments may inhibit BCG viability.

Dosage and Treatment Schedule

The recommended dose for immunotherapy is 4 vials, 120 mg, or approximately 1 x 10⁸ CFU. This dose should not be exceeded.

The standard schedule of treatment consists of 6 instillations, with an interval of one week between each instillation. This treatment schedule may be repeated once in the same episode, if no response is achieved after the first immunotherapy treatment. Maintenance therapy may be recommended for certain high risk patients.

Reconstitution and Route of Administration

Intravesical instillation (only): 1 vial of BCG Culture SSSI (preparative, preservative-free 0.9% NaCl), in a sterile area (preservative-free isotonic saline is transferred to a 50 ml bag containing 2-3 ml sterile saline). The resuspended solution may be kept for up to 6 hours at room temperature and for up to 24 hours refrigerated at 2-8°C. If the suspension is kept refrigerated it must be completely dry before piercing with a syringe. After reconstitution, the suspension is clear and slightly cloudy.

The suspension must be administered intravesically. Care must be taken in order to re-suspend clusters of freeze-dried bacteria. Transfer the contents of the 4 vials to a 50 ml syringe. Add a further volume of 2-3 ml from a 50 ml bag containing preservative-free isotonic saline to the suspension, and the contents are homogenised by GENTLE ADDITION of the saline suspension into the vial. The suspension has been reconstituted at the time of the infusion bag. This process is repeated 3 more times, until the contents of all 4 vials have been resuspended into the 50 ml infusion bag.

The suspension should be used as soon as possible after preparation (less than 4 hours), and must not be exposed to light.

As expected insertion of a urethral catheter must be performed atraumatically to avoid damage to the surface of the urethra and bladder. Treatment with BCG Culture SSSI should be postponed at least 7-14 days if the urethra becomes traumatised during catheterisation, as a lesion in the urethral mucosa increases the risk of systemic BCG infection (see also Contraindications and Warnings).

The 50 ml suspension of BCG Culture SSSI is slowly instilled into the empty bladder, taking care not to force the flow. At the end of the instillation, the bladder is thoroughly irrigated with saline, and the catheter is removed, and the patient is instructed to retain the suspension in the bladder for 2 hours, if possible. Restriction of fluid intake 3-6 hours prior to instillation may be recommended for patients with a limited bladder capacity. As BCG Culture SSSI is not a biodegradable material, the suspension may be voided in a normal manner, and no special precautions are necessary.

Contraindications and Warnings

- Patients with a limited bladder capacity. As BCG Culture SSSI is not a biodegradable material, the suspension may be voided in a normal manner, and no special precautions are necessary.

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