Contemporary Intravesical Therapy for Non-Muscle Invasive Bladder Cancer

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Abstract

• Urinary Bladder Cancer is the fourth most common cancer in men and the ninth most common cancer in women with an incidence of 73,500 new cases per year and a prevalence population of nearly 600,000 patients.
• The principal form of therapy for non-muscle invasive (superficial disease) is transurethral resection [TUR] of the tumor followed by intravesical therapy which can be administered immediately after surgery or on a weekly basis usually for six weeks.

Abstract

• Contemporary treatment chemotherapy agents are generally limited to Mitomycin C and Valrubicin. Bacille Camette Guerin [BCG] is an attenuated mycobacteria initially developed as a vaccine for tuberculosis which elicits an immune reaction in the bladder and very effective as a treatment for higher risk disease. It is a live bacteria and cannot be administered after surgery or in the presence of gross hematuria.

Abstract

• Generally chemotherapeutic agents and immune agents are given weekly for 6 weeks based on authority opinion. Chemotherapy agents generally reduce the frequency of tumor recurrence by 17% and have little or no impact on disease progression. BCG can demonstrate a 40-80 percent response rate as a therapeutic (eradicate remaining tumor) or prophylactic (reduce recurrence after total tumor removal) agent.

Abstract

• Immediate installation of chemotherapy after TUR may result in a decrease in tumor recurrence up to a 39% but should not be done when bladder perforation is suspected, a large area of the bladder is resected or if the patient has a history of irritative voiding. Other methods of optimizing intravesical chemotherapy include pH balance of the urine for maximal tissue absorption and experimental work in electromotive transport of chemotherapy to provide deeper tissue penetration.

Abstract

• A general trend in the treatment of high risk disease has been to consider cystectomy and some form of urinary diversion earlier in those patients who do not appear to respond to therapy rather than repeat treatments.
Bladder Cancer Advocacy

Objectives

1. Understand the impact of bladder cancer on the population and the principle form of treatment for this disease.
2. Develop familiarity with the principle agents for treating this disease and their effectiveness.
3. Develop an acquaintance with the newer methods of treatment, and considerations in the treatment of resistant or refractory disease.

Epidemiology

- Estimated 73,510 new cases in 2012.
- Men 55,600. Women 17,910.
- 14,880 cancer related deaths and 585,390 representative of bladder cancer survivors.
- Second most common genitourinary malignancy
- Men: 4th most common (7% of male cancers) 7th cause of death.
- Women: 10th most common (2% of female cancers) 10th cause of death.

Epidemiology

- Male: Female ratio 3:1
- Two thirds >65 years of age, rare under 30. Median age at diagnosis is 73.
- One half as common in the African American population.
- Women and African Americans generally have a poorer survival prognosis.
- Over the past two decades, there has been approx. 40% increase in the overall incidence.

Etiology

- Overwhelmingly a sporadic disease
- Tobacco exposure may increase risk by 2-3 fold
- Environment & Occupational exposure have a role [Arsenic in drinking water & dye, textile printing, rubber and leather industries]
- Aniline dyes
- Cyclophosphamide (acrolein) 9X and isofosfamide
- Ionizing Radiation
- Chronic Infection [stones, indwelling catheter]

Etiology

- Phenacetin ingestion
- Dietary Fat
- Chinese herb- Arisolochia fangchi, used in weight reduction programs
- Early data suggests possible link to Pioglitazone
- Genetic predisposition – Hereditary component may be related to genes that handle metabolism of carcinogens
Role of the APP in Screening and Diagnosis

- Prompt Referral
- Gross Hematuria
- Asymptomatic Microscopic Hematuria (AMH)
- AMH in patients with irritative voiding symptoms, current or past tobacco use, chemical exposures
- Irritative voiding symptoms
- Abnormality on Cross Sectional Imaging, i.e. bladder mass, renal collecting system mass

Screening Guidelines for the Advanced Practice Provider

- DIAGNOSIS, EVALUATION and FOLLOW-UP OF ASYMPTOMATIC MICROHEMATURIA (AMH) IN ADULTS: American Urological Association Guideline (AUA) GUIDELINE 2012
  - Guidelines are based on Expert Opinion, Clinical Principles, and Recommendations – Evidence Strength Grade C
  - Guideline Statements include nineteen recommendations

Hematuria Guidelines

- Asymptomatic microhematuria (AMH) is defined as three or greater red blood cell (RBC) per high powered field (HPF) on a properly collected urinary specimen in the absence of an obvious benign cause. A positive dipstick does not define AMH, and evaluation should be based solely on findings from microscopic examination of urinary sediment and not on a dipstick reading. A positive dipstick reading merits microscopic examination to confirm or refute the diagnosis of AMH.

Hematuria Guidelines

- Assessment should also include a careful history, physical examination, and laboratory examination to rule out benign causes of AMH
  - Infection
  - Menstruation
  - Vigorous Exercise
  - Medical Renal Disease
  - Viral Illness
  - Trauma

Hematuria Guidelines

- A concurrent nephrologic workup does not preclude the need for a urologic evaluation. Presence of dysmorphic RBC’s, proteinuria, cellular casts, or renal insufficiency

Hematuria Guidelines

- Microhematuria that occurs in patients taking anticoagulants requires a urologic and nephrologic evaluation regardless of the type and level of anticoagulation therapy

Hematuria Screening

<table>
<thead>
<tr>
<th>Tumor grade/stage</th>
<th>Unscreened</th>
<th>Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Low grade NMIBC</td>
<td>290 56.8</td>
<td>11</td>
</tr>
<tr>
<td>52.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade NMIBC</td>
<td>99 19.4</td>
<td>9</td>
</tr>
<tr>
<td>42.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Invasive</td>
<td>122 23.9</td>
<td>1</td>
</tr>
<tr>
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</tbody>
</table>
Hematuria Evaluation
Upper Tract Evaluation
- CTU – Multiphasic computed tomography (CT) urography both with and without (IV) contrast, to evaluate the renal parenchyma to rule out a renal mass, and the urothelium of the upper tracts.
- CTU is the imaging procedure of choice as it has the highest sensitivity and specificity.

Hematuria Evaluation
Upper Tract Evaluation
- MRU- Magnetic Resonance Urography is recommended for patients with relative or absolute contraindications such as renal insufficiency, contrast allergies, or pregnancy.
- Alternate Evaluations
- MRI w/ retrograde pyelograms (RPG’s)
- Non-contrast CT or Renal US w/ retrograde pyelograms (RPG’s)

Upper Tract Evaluation
- CTU
- MRU

Lower Tract Evaluation
- A cystoscopic examination is required for the evaluation of hematuria, both asymptomatic microhematuria and gross hematuria, irritative bladder symptoms, and abnormality on imaging, ie bladder or ureteral lesion.
- A Cystoscopy should be performed for on all patients greater than age 35 years and older, younger patients at the Urology Provider’s discretion.

Lower Tract Evaluation
- Cystoscopic Examination – Examination of the bladder using a lighted telescope
- Picture

Urine Cytology
- Urine Cytology has a low sensitivity and specificity in detection as it relates to the stage of the disease.
- Low grade tumors are less likely to be detected with urine cytology.
- Urine cytology is more likely to detect high grade tumors.
- A cytology finding of “urothelial carcinoma” necessitates further work up.
Pathology Review

- Pathology Review
- New Cancer Diagnosis
- Treatment Recommendations
- Surveillance Recommendations

Pathology

- Over 90% of lesions are transitional cell carcinoma
- 5-7% of lesions are pure squamous cell. Associated with chronic irritation [stones, foley catheter, Schistosomiasis]
- 1-2% Adenocarcinoma [urachal carcinoma, cystitis glandularis]. Rule out metastatic source.
- Metaplastic elements of squamous or adenocarcinoma in TCC is different than pure tumor devoid of TCC

Bladder Cancer Staging

- Tumor Depth Stong-Jewett UICC/AJCC
  - Urothelium O pTa
  - Carcinoma in situ pTis
  - Lamina Propria A pT1
  - Superficial Detrusor B1 pT2a
  - Deep Detrusor B2 pT2b
  - Perivesical fat [micro] C pT3a

Bladder Cancer Staging

- Non Muscle Invasive TCC

Non-muscle invasive TCC
Bladder Cancer - Diagnosis

Urovysion – Chromosome “painting” or

Staging – Role of Re-TUR

Bladder Cancer - Natural History

Guidelines and Best Practice Recommendations

Trans-urethral resection of Bladder Tumor (TURBT)
### Tumor Progression

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Probability of Recurrence in 5 years</th>
<th>Probability of Progression to MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50%</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50-70%</td>
<td>Moderate-High</td>
</tr>
<tr>
<td>Tis</td>
<td>50-90%</td>
<td>High</td>
</tr>
</tbody>
</table>

NCCN Clinical Practice Guidelines in Oncology 2009

- Low Risk
  - Solitary, small volume, low grade Ta
  - Single immediate chemotherapeutic instillation after TURBT is recommended for patients with primary, small solitary low grade tumors, except for those with obvious or suspected bladder wall perforation.

- Intermediate Risk
  - Multiple or Recurrent low-grade tumors
  - Multifocal and/or large volume low grade Ta
  - High risk of recurrence, low risk of progression

- High Risk
  - High Grade Ta, All T1, and CIS
  - Repeat Turbt 2-6 weeks after initial resection
  - Intravesical BCG induction plus maintenance for 1 year
  - Immediate Cystectomy for highest risk - i.e., multiple recurrent high grade tumors, high grade T1 tumors with concomitant CIS

- High Risk
  - Intravesical BCG plus maintenance for at least 1 year
  - Continue w/ 3 weekly boosters or additional 6 week course of BCG, or cystectomy
  - No complete response at 6 weeks, radical cystectomy
  - w/o treatment 54% progress to MIBC
INTRAVESICAL AGENTS

MITOMYCIN C

EPIRUBICIN

DOXORUBICIN

MITOXANTRONE

VALRUBICIN

THIOTEPA

GEMCITABINE

TAXANES

Mitomycin C

- An Alkylating agent that inhibits DNA synthesis. The most frequently encountered side effect is chemical cystitis manifested by frequency, urgency, and dysuria lasting several weeks and sometimes months.

40mg dose weekly x 6 weeks

Valrubicin

- Valrubicin is an anthrocycin –like agent (doxorubicin) which is lipohillic for greater tissue penetrance. It is FDA approved for those patients with BCG refractory carcinoma in situ or those patients incapable for unwilling to undoing cystectomy. It has a 27% response rate with a 20% complete response over approximately 18 months.

Approved in 1998 then withdrawn from market due to manufacturing impurity issues. Reintroduced in 2009 after receiving FDA approval

- Indicated for BCG refractory CIS

- Patients with multiple comorbidities, and when the mortality and morbidity of immediate cystectomy may be unacceptable

Gemcitabine

- Latest study by Sternberg et al., (2013) Intravesical gemcitabine for high risk NMIBC after BCG treatment failure resulted in a complete response in 27of 69 patients and hade delayed time to cystectomy.

- Intravesical gemcitabine therapy for NMIBC (BJUI 2011 Shelley et al) A single study suggests that multiple doses of intravesical gemcitabine reduces tumor recurrences to a greater extent than a single dose.

- No more than two induction series of BCG intravesical therapy is recommended.

- Semisynthetic analog of doxorubicin

- 18% rate achieved a complete recurrence free response. About 1 in 5 study patients were disease free at 3 months. 29% clinical benefit

- w/o complete response at 3 months – reconsider Cystectomy
**Gemcitabine**

- When gemcitabine was compared to BCG, gemcitabine had similar efficacy with intermediate-risk patients, less effective in high-risk patients, and superior in BCG-refractory patients.
- Gemcitabine 2 gms twice weekly x 3 weeks, separated by a week of rest, for a total of 12 installations.
- More studies are needed to determine the role of intravesical gemcitabine.

**Prophylactic Intravesical Therapy Percentage Recurrence**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Control %</th>
<th>Drug %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiotepa</td>
<td>62</td>
<td>45</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>52</td>
<td>37</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>56</td>
<td>38</td>
</tr>
</tbody>
</table>

- The difference is approximately 17% in all cases which drops to 6% long term.

**Single Installation Meta analysis**

- 7 randomized trials TaT1 tumors
- Median follow-up 3.4 years
- 39% decrease in the odds of a recurrence [48.4% vs 36.7%] with TURBT + Chemo vs. TURBT alone
- Single tumor [OR 0.61] less effective for patients with multiple lesions

**Intravesical Chemotherapy Therapy Conclusions**

- An ideal intravesical agent does not exist.
- **Prophylactic benefit is real yet small [14-17%].**
- Benefit demonstrated in first 3 years of therapy
- Little effect on tumor progression
- Single instillation may confer recurrence protection 35%

**Bladder Cancer**

**Treatment of NMIBC with Immunotherapy**

- Attenuated strain of mycobacterium
- Anticancer activity noted in some tumor systems [melanoma]
- Factors for success: limited tumor burden immune status proximity of tumor cells
- 1976 - Morales demonstrates clinical efficacy
- Bacillus Calmette-Guerin immunotherapy is currently the most effective treatment on
BCG

- Exact mechanism of action is unknown
- Tumor contact with BCG is required. This is mediated by novel fibronectin receptors and classic integrin receptors
- Appears that Th1(T-helper cell) response is significant in BCG activity
- IL 12 and INF gamma up regulated
- NOS induction by BCG may also play a role
- PMN response may also be important

Meta analysis of BCG Maintenance

- Effect on progression noted only in trials where some form of maintenance was employed n=1400
- 37% odds reduction OR 0.63, 95% CI [0.51to 0.79],
- p = 0.00004

BCG SWOG TRIAL 6 +3

Meta Analysis of Disease Specific Survival

- Information from 8 trials
- Bladder cancer death 5.6% with BCG and 7.7% for controls
- OR 81, 95% CI 58 to 1.13, P = 0.2

BCG Complications

- LUT Symptoms 80-90%
- Low-Grade Fever 60-80%
- Arthalgia 0.6%
- Pneumonia/Hepatitis 0.7%
- Prostatitis 0.9%
- Bladder Contraction 0.9%
- BCGosis 1.0%
- BCG Sepsis rare

BCG Treatment Failure

- Treatment failure after one course
  - What is the clinical cost/benefit of retreatment?
  - 7% progression rate
  - 77% complete response
- Treatment failure after two courses
  - 30% progression rate over 3-5 years
  - 50% metastatic disease over 3-5 years
  - Role for cystectomy
Interferon

• A immunotherapy agent which may be given alone or in conjunction with BCG and has a synergistic effect when used with BCG.
• Interferon A (Intron A) 50milions/iu
• Small treatment advantage

BCG Alternatives

• BCG and interferon can be administered simultaneously
• 1/3 dose BCG with 50 million units of INFa2B followed with boosters of 1/10,1/30, or 1/100 BCG [ N= 40 patients]
• Large scale trials in progress (suggests 10-15% improvement in BCG naive or responsive cases), serial administration also studied.

On the Horizon

• Mycobacterial wall products
• Vaccines and Gene therapy
• Photodynamic Therapy

Treatment Considerations

• Hold Treatment for Acute UTI, Hematuria, Febrile Illness, and severe abdominal pain
• Monitor LFT’s for BCG Immunotherapy
• Monitor CBC for Mitomycin, Valrubicin, Gemcitabine Chemotherapy and Interferon
• Send a Urine Culture if a UTI is suspected.
• Ciprofloxacin deactivates BCG. Use alternate Antibiotic therapy

Surveillance

• Presently tumor markers do not direct follow up interval
• Upper tract recurrence is classically 0.002-2.4%
• In BCG era upper tract recurrence 13-25%
• Cumulative risk can be higher over 15 years
• Continual follow up of upper tracts required

Surveillance

• Cystoscopic Surveillance is classically every three months x for 1 year until disease free, then q 6 months, then annually.
NMIBC Treatment Guidelines

• AUA American Urological Society
• EAU European Urological Society
• NCCN National Comprehensive Cancer Network

Office Follow Up for the Advanced Practice Provider

Bladder Cancer Patients
• Confirm adherence to Bladder Cancer Surveillance with Urologist /Urology Provider.

Persistent Asymptomatic Hematuria Patients
• Two consecutive negative annual urinalysis- no further urinalysis needed
• Persistent AMH after negative workup- yearly urinalysis
• Persistent or recurrent AMH after negative urologic workup- repeat evaluation within three

Case Studies

• 70 year old Homemaker
• 2ppd Smoker x 50 years
• UA demonstrates Microscopic Hematuria

Case Studies

• 55 yr old Printer with NMIBC
• Pathology shows HGT1 & Associated CIS
• Failed Induction Course of BCG X 6

Pre/Post Test

1. Low Grade Bladder Cancer typically progresses to High Grade Disease. True or False
2. Low Grade Bladder Cancer is less likely to recur than HG Bladder Cancer. True or False
3. There is an increased chance that HGT1 bladder Cancer associated with CIS will lead to muscle invasive disease. True or False

Pre/Post Test

4. Intravesical Chemotherapy and Immunotherapy are equal in effectiveness in regard to tumor progression. True or false
5. The first post treatment cystoscopic examination and surgical pathology findings are a good indicator of disease status. True or False
Suggested Readings


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