Bladder Cancer: Perioperative Chemotherapy

Andrea L. Harzstark, MD
Assistant Professor of Medicine
University of California, San Francisco
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TCC Prognosis

- Pathologic stage is most important prognostic factor
- 50% of pts with muscle invasive disease develop metastases within 2 yrs
  - pT2 60-80% 5 yr OS
  - pT3 30-50%
  - pT4 0-20%
  - pN1 50%
  - pN2,3 0-20%

Neoadjuvant Chemotherapy for Muscle Invasive Cancer

- Improvements in pT0, T1 rates affect long term outcome
  - 125 pts on cisplatin-based neoadjuvant therapy, median f/u 25 months, 91% of pts with pT1 or better disease at cystectomy were disease free, 37% of pT2 or worse

- Advantages:
  - Early systemic treatment
  - Improved p0 rates at cystectomy
  - In vivo chemosensitivity testing
  - Survival benefit
  - Improving ease of surgery

- Disadvantages:
  - Delays definitive therapy
  - Chemotherapy toxicity
  - Relies on clinical staging

Raghavan, J Urol 1985
Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Eligibility</th>
<th>N</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/EORTC</td>
<td>CMV</td>
<td>T2-T4a, N0-Nx, M0</td>
<td>976</td>
<td>pCR 33% vs. 12%</td>
<td>Surgery (50%) or radiation allowed</td>
</tr>
<tr>
<td>INT 0080</td>
<td>MVAC</td>
<td>T2-T4a, N0M0</td>
<td>317</td>
<td>pCR 38 vs 15%</td>
<td>13 yrs required to complete accrual, 1/3 with grade 3 heme or GI toxicity</td>
</tr>
<tr>
<td>Italian Bladder Tumor Study</td>
<td>MVEC</td>
<td>T2-T4, N0M0</td>
<td>171</td>
<td>No difference in DFS or OS</td>
<td>Never published in final form, accuracy of clinical staging 42%</td>
</tr>
<tr>
<td>Nordic 2</td>
<td>Cisplatin/MTX</td>
<td>T2-T4a, NxM0</td>
<td>317</td>
<td>pCR 26.4% vs. 11.5% (p=0.001), 5 yr OS 53 vs. 46% (not stat sig)</td>
<td></td>
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</table>

- Underpowered randomized trials with varying regimens leading to inconclusive results
- Meta-analysis: 3005 pts on 11 studies
  - 13% relative risk reduction in death at 5 years
  - Absolute benefit of 5% reduction in death at 5 years (CI 1%-9%)
  - 5-year survival improves from 45% to 50% with platinum-based combination chemotherapy
  - Survival curves separate at 6 months and remain apart thereafter

Standard in neoadjuvant setting is MVAC
Extrapolation from metastatic setting to use gemcitabine/cisplatin
pT0 response does not obviate need for definitive local therapy
- In one study, clinical T0 response after MVAC in 57% but only 30% pT0 at cystectomy
Randomized Phase III Study
Gemcitabine/Cisplatin vs. MVAC

GC
- Gemcitabine 1000 mg/m² day 1, 8 and 15 every 28d
- Cisplatin 70 mg/m² day 2 every 28d

MVAC
- Methotrexate 30 mg/m² day 1, 15 and 22 every 28d
- Vinblastine 3 mg/m² day 2, 15 and 22 every 28 days
- Doxorubicin 30 mg/m² day 2 every 28 days
- Cisplatin 70 mg/m² day 2 every 28 days

Endpoint
Primary Endpoint
- Overall survival
  - Designed to detect 33% OS difference
    with 2-sided $\alpha = .05$ and power 80%

Efficacy

<table>
<thead>
<tr>
<th></th>
<th>G-C</th>
<th>MVAC</th>
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<tbody>
<tr>
<td>Overall Survival</td>
<td>13.8 months</td>
<td>14.8 months</td>
</tr>
<tr>
<td>Response Rate</td>
<td>49.4%</td>
<td>45.7%</td>
</tr>
<tr>
<td>CR</td>
<td>12.2%</td>
<td>11.9%</td>
</tr>
<tr>
<td>PR</td>
<td>37.2%</td>
<td>33.8%</td>
</tr>
<tr>
<td>SD</td>
<td>33.5%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Median TTP</td>
<td>7.4 months</td>
<td>7.4 months</td>
</tr>
<tr>
<td>Median TTF</td>
<td>5.8 months</td>
<td>4.6 months</td>
</tr>
</tbody>
</table>

Overall Survival
MVAC Chemotherapy

- Substantial toxicity with MVAC
  - Neutropenic sepsis
  - Mucositis
  - Nausea/Vomiting
  - Renal insufficiency
  - Cardiotoxicity
  - Neurotoxicity

- Toxic death rate of 3-4% (pre-growth factor era)
- Long term disease free survival 3.7% at 6 years

Adjuvant Chemotherapy

- Advantages
  - Can risk stratify based on pathology in deciding whom to treat, limiting toxicity
  - Does not delay definitive therapy (cystectomy)

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<tr>
<td>USC</td>
<td>CISCA</td>
<td>pT3/4 and/or N+</td>
<td>91</td>
<td>OS 4.3 vs 2.4 yrs (p=0.0062)</td>
<td>3 yr OS not stat sig improved</td>
</tr>
<tr>
<td>German</td>
<td>MVAC or MVEC</td>
<td>pT3b, pT4a and/or positive regional LNs</td>
<td>83</td>
<td>Improvement in PFS, EFS, OS (stat sig)</td>
<td>No chemo at relapse</td>
</tr>
<tr>
<td>Swiss</td>
<td>Cisplatin</td>
<td>pT2+</td>
<td>77</td>
<td>5 yr OS 57 vs 54%</td>
<td></td>
</tr>
<tr>
<td>Stanford</td>
<td>CMV</td>
<td>pT3b, T4, LN+</td>
<td>55</td>
<td>Median OS 63 vs 36 mos (not stat sig), 5 yr OS 40 vs. 38%</td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td>Cisplatin/MTX</td>
<td>pT2+, N-</td>
<td>83</td>
<td>OS and progression curves reported to diverge</td>
<td>No statistical analyses reported</td>
</tr>
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Adjuvant Chemotherapy

- Few well designed clinical trials, small numbers of patients
- Multiple studies closed for poor accrual (EORTC, Spanish Intergroup, CALGB, Italian Multicenter)
- P53 positive study (SWOG/USC) closed for futility
- Certain subsets of patients appear to benefit from adjuvant therapy:
  - pT3-pT4
  - Node positive
- No standard regimen, usually 4 cycles gemcitabine/cisplatin
Neoadjuvant Vs. Adjuvant Chemotherapy

- No studies have directly compared
- 140 pts with locally advanced TCC: 2 pre-op + 3 post-op vs. 5 post-op
  - Similar outcomes in both groups
  - Lower incidence of positive margin in pre-op group (11 vs. 2%)
  - Lower incidence of LN metastases in pre-op group (36 vs. 22%)

Renal Insufficiency

- Carboplatin may be substituted for cisplatin in patients with impaired renal function, but is likely not as effective
- Survival of these patients is inferior to patients with normal renal function
- Gemcitabine/carboplatin is most commonly used bladder cancer regimen in the US

Peri-Operative Chemotherapy: Rarely Used

- Estimate that peri-operative chemotherapy used in 10% of patients for whom it’s recommended... Why?
  - Elderly patient population with multiple comorbidities
  - Less value to carboplatin-based therapy
  - Referral patterns
  - Patients reluctant to undergo chemotherapy
  - Absolute benefit is small (although similar for other malignancies)
    - Benefit of adjuvant therapy in breast cancer 5-10%
    - Benefit of adjuvant therapy in colon cancer 5%