Neoadjuvant Chemotherapy Prior to Radical Cystectomy (Con Argument)

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Neoadjuvant Chemotherapy (NAC) in MIBC

Goals today are simple:

#1 – Neoadjuvant Chemotherapy (NAC) is not appropriate or necessary for all patients prior to radical cystectomy

#2 – A more selective approach to NAC avoids unnecessary delay in local therapy as well as potential harms/toxicity, while allowing adjuvant chemotherapy for those with adverse pathologic features
Factors in the Decision

- Evidence
- Patient Factors
- Toxicity
- Selective Approach
Evidence for use of NAC prior to Radical Cystectomy

Level of Evidence

Endorsed by Guidelines
Neoadjuvant Chemotherapy (NAC) in MIBC

• Level 1 evidence from the SWOG-8710 demonstrated improved survival with neoadjuvant MVAC in patients with MIBC (cT2-T4aN0M0) undergoing cystectomy

• NAC followed by RC improved survival over RC alone
  – Median survival: 77 vs 46 months

• NAC offered to ALL eligible patients, with no attempt to select those who might be best served

Neoadjuvant Chemotherapy: SWOG 8710

Neoadjuvant Chemotherapy (NAC) in MIBC

• Although overall survival benefit was seen in the entire cohort, the most dramatic improvement in was in those with more advanced disease (patients with ≥T3)

Neoadjuvant Chemotherapy (NAC) in MIBC

- Meta-analysis of 10 randomized clinical trials of NAC (2,688 pts) and compared platinum-based NAC plus definitive local therapy to definitive local therapy alone
- Confirmed OS benefit of platinum-based NAC
- 5-yr OS: 50% for platinum-based NAC vs. 45% for local therapy alone (HR 0.87; 95% CI 0.77-0.97)
- Absolute benefit in RFS: 7% for platinum-based NAC (HR 0.81; 95% CI 0.74-0.90)

Neoadjuvant Chemotherapy: Meta-analyses

No Substitute for Cisplatin-based NAC

• There is no proven benefit for non-cisplatin-based NAC in bladder cancer outside the context of clinical trial.

• Therefore, patients who are ineligible or who may not tolerate cisplatin should proceed directly to radical cystectomy or referred to a clinical trial.

• Adherence to Guidelines and Level I evidence is important for optimal patient care.
Not all Patients are Eligible for NAC

- More than 50% of patients are ineligible for cisplatin because of a poor PS, impaired renal function, or comorbidities
- In addition, patients may not be eligible due to other factors not measured in RCT’s

But, Not all Patients Qualify

- Despite Level I evidence, not all patients qualify for cisplatin-based NAC
- Patients must be carefully screened for cisplatin eligibility based on consensus factors including:
  - Impaired Renal Function (GFR < 50-60 mL/min)
  - Impaired Performance Status (ECOG PS ≥ 2)
  - Heart Disease: NYHA ≥ class III heart failure
  - Grade ≥ 2 Neuropathy
  - Significant Hearing Loss
• NAC is recommended for cT2-T4aN0M0 and should always be platinum-based (Gr A)
• NAC is not recommended for pts with PS >2 and or impaired renal function (Gr B)
• In case of progression during NAC, this treatment should be discontinued (Gr B)
• Clinicians should not prescribe carboplatin-based neoadjuvant chemotherapy for clinically resectable stage cT2-T4aN0 bladder cancer.
  — **No Carboplatin** (cisplatin ineligible)

• Patients ineligible for cisplatin-based neoadjuvant chemotherapy should proceed to definitive locoregional therapy.
  — **Proceed to definitive treatment**

auanet.org
And, Not all Tumors Respond to NAC

Molecular Subtypes of Urothelial Bladder Cancer: Results from a Meta-cohort Analysis of 2411 Tumors

Tuan Zea Tan a,e, Mathieu Rouanne b,c, Kien Thiam Tan d, Ruby Yun-Ju Huang a,c,e, Jean-Paul Thiery a,c,j

Results suggest that primary and secondary MIBC have disparate clinical outcomes and differential responses to cisplatin-based NAC. Genomic analysis reveal primary MIBC, but not secondary MIBC, is more likely to harbor likely pathogenic ERCC2 mutations predicted to be sensitizing to cisplatin-based chemotherapy.

Urothelial carcinoma (UC) meta-cohort revealed six molecular subtypes.
Selective Approach

Can we identify patients who will do well with radical cystectomy alone?
Can we predict who will benefit from NAC?
Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy

Stephen H. Culp,* † Rian J. Dickstein,* † H. Barton Grossman,‡ Shanna M. Pretzsch,* Sima Porten,* Siamak Daneshmand,§ Jie Cai,* Susan Groshen,* Arlene Siefker-Radtke,* Randall E. Millikan,* Bogdan Czerniak,* Neema Navai,* Matthew F. Wszolek,* Ashish M. Kamat† ‡ and Colin P. N. Dinney† ‡ **

OS (47% vs. 65%; P < .001)

CSS (64% vs. 84%; P < .001)
Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy


Resectable Urothelial cancer

Low risk ≤ cT2 → Radical cystectomy

High Risk
• Lymphovascular invasion
• Hydronephrosis
• 3-D mass on EUA (cT3b)
• cT4a
• Micropapillary
• Neuroendocrine

Neoadjuvant chemotherapy → Radical cystectomy

Figure 4. Neoadjuvant platform for clinical based staging and therapy for bladder cancer.
Eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4 and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy.

— Moderate Recommendation; Evidence Level: Grade C

- All adjuvant chemotherapy trials underpowered, terminated early
- Meta-analyses have demonstrated possible benefit (quality of data variable)
Support for Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>ACT Treated</th>
<th>LOE</th>
<th>Result (95% CI)</th>
<th>OS</th>
<th>CSS</th>
<th>DFS</th>
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</thead>
<tbody>
<tr>
<td>ABC Collaboration³</td>
<td>Individual patient data meta-analysis from 6 RCTs</td>
<td>491</td>
<td>246</td>
<td>2a</td>
<td>HR,</td>
<td>0.75 (0.60-0.96)</td>
<td>NA</td>
<td>HR, 0.68 (0.53-0.89)</td>
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<tr>
<td>Ruggeri et al⁴</td>
<td>Literature-based meta-analysis from 5 RCTs</td>
<td>350</td>
<td>167</td>
<td>2a</td>
<td>RR,</td>
<td>0.74 (0.62-0.88)</td>
<td>NA</td>
<td>RR, 0.65 (0.54-0.78)</td>
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<tr>
<td>Svatek et al⁴</td>
<td>Retrospective cohort study from 11 high-volume centers</td>
<td>3947</td>
<td>932</td>
<td>2c</td>
<td>NA</td>
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<tr>
<td>Leow et al³⁵</td>
<td>Literature-based meta-analysis from 9 RCTs</td>
<td>945</td>
<td>475</td>
<td>2a</td>
<td>HR,</td>
<td>0.77 (0.59-0.99)</td>
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<td>HR, 0.66 (0.45-0.91)</td>
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<tr>
<td>Booth et al²</td>
<td>Population-based retrospective cohort study</td>
<td>2809</td>
<td>541</td>
<td>2c</td>
<td>HR,</td>
<td>0.71 (0.62-0.81)</td>
<td>HR, 0.73 (0.64-0.84)</td>
<td>NA</td>
</tr>
</tbody>
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*LOE: Quality of evidence*
A 25% risk reduction in death, with an absolute improvement in survival of 9% at 3 years

Toxicity

What is the toxicity?

Does it limit or prevent radical cystectomy?
Neoadjuvant Chemotherapy Toxicity

• Grade 3 and 4 toxicity in 35% and 37% of patients, respectively, mostly related to granulocytopenia and mucositis

• International Collaboration of Trialists reported similar grade 3 and 4 hematological toxicity in patients treated with cisplatin, methotrexate and vinblastine

Neoadjuvant Toxicity does not Reduce RC Rates

- Despite toxicity, radical cystectomy rates are similar between groups in RCT’s

- In SWOG-8710, the planned cystectomy was performed in 82% of NAC and 81% of the cystectomy group

NAC use increased from 10.1% to 20.8% (p=0.005), while AC remained stable between 18.1% and 21.3% (p=0.68)
Factors in the Decision

- Evidence
  - Level 1a
  - Cis-platin Only

- Patient Factors
  - Limits Eligibility

- Toxicity
  - Acceptable but substantial

- Selective Approach
  - Practical & Feasible
Against NAC for All: Conclusions

- Neoadjuvant chemotherapy should **Not** be offered to all patients with MIBC
- MIBC patients with low risk features should move forward with definitive local therapy (radical cystectomy)
- Patients ineligible for cisplatin therapy should not receive NAC outside context of a clinical trial
- Adjuvant therapy should be considered for those patients with adverse pathologic features following radical cystectomy
The Future of Neoadjuvant Chemotherapy

"Here's my sequence..."

New Yorker, 2000