Neoadjuvant/Adjuvant Chemotherapy: Are We Ready to Accept NAC as the Gold Standard?

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Disclosures

• Clinical trials
  – Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), UroGen, Viventia

• Consultant
  – BioCancell, UroGen, Vaxiion

• Advisory Board
  – BioCancell, miR Scientific, QED Therapeutics, UroGen

• MSD Korea, Dava Oncology – honoraria
Overview

• Why integrate peri-operative chemotherapy and radical cystectomy
• Evidence supporting NAC
• Limited evidence supporting Adjuvant
• One size fits all
• Invent the future: Precision medicine
Metastatic Bladder Cancer
M-VAC vs Gemcitabine/Cis-platin - Overall Survival

This trial has established Gem/Cis as a viable treatment option

Updated (Ann Oncol 2006) results similar

von der Maase, H et al J Clin Oncol 23:4602, 2005
### SWOG 8710: Overall Survival by Treatment Arm

<table>
<thead>
<tr>
<th>ARM</th>
<th>No. Pts.</th>
<th>No. Pts. Dead</th>
<th>Median Survival</th>
<th>%5 Yr Survival</th>
<th>p Value (log-rank, 1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>154</td>
<td>96</td>
<td>43.2 mos</td>
<td>42.1%</td>
<td></td>
</tr>
<tr>
<td>MVAC</td>
<td>153</td>
<td>90</td>
<td>74.7 mos</td>
<td>57.2%</td>
<td>0.044</td>
</tr>
</tbody>
</table>
Neoadjuvant Chemotherapy Improves pCR (P0) rate

<table>
<thead>
<tr>
<th>Source</th>
<th>CTx + cyst</th>
<th>cyst alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/International (CMV)</td>
<td>32.5%</td>
<td>12.3%</td>
</tr>
<tr>
<td>SWOG (MVAC)</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>Nordic II (MTX/Cisplatin)</td>
<td>26.4%</td>
<td>11.5</td>
</tr>
<tr>
<td>MSKCC (GC)</td>
<td>26%</td>
<td>NA</td>
</tr>
<tr>
<td>MSKCC (M-VAC)</td>
<td>28%</td>
<td>NA</td>
</tr>
<tr>
<td>Columbia (MVAC)</td>
<td>31%</td>
<td>NA</td>
</tr>
<tr>
<td>Columbia (GC)</td>
<td>25%</td>
<td>NA</td>
</tr>
<tr>
<td>CCF (GC)</td>
<td>7%</td>
<td>NA</td>
</tr>
<tr>
<td>International consortium</td>
<td>NA</td>
<td>5.1%</td>
</tr>
</tbody>
</table>
Higher risk of relapse:
- 3-D mass on EUA
- Prostatic stroma, vaginal wall involvement (T4a)
- LVI - increased risk of occult nodal involvement
- Hydronephrosis - Increased risk of extra-vesical extension
- Micropapillary tumor
- Small cell neuroendocrine tumor

SWOG 8710 Neoadjuvant M-VAC- Benefit cT2 vs. cT3-T4a

*Pts with cT2 also benefit from neoadjuvant chemotherapy*

![Median survival graph]

- cT2: 105 vs. 75 mos
- cT3-4a: 65 vs. 24 mos

Low Risk Patients Benefit from NAC

- Mayo Clinic 1980-2016
- RC for cT2-4N0; n = 1931
- Low risk (n = 1025; 104 with NAC)
- NAC in LR patients was associated with greater odds of pT0 (OR 3.05; \( p < 0.001 \)) and < pT2 (OR 2.53; \( p < 0.001 \)) disease, but was not significantly associated with CSS (\( p = 0.31 \))
- “These data support offering NAC to all eligible MIBC patients irrespective of risk classification, and may aid in informed discussion of treatment sequencing for LR patients.”

Lyon, et al World J Urol epub 11/13/19
Neo-adjuvant Chemotherapy Meta Analysis
5% Survival Advantage

- Individual patient data from 6 randomized trials
- 9% survival benefit with platinum based combination chemotherapy

Neoadjuvant chemotherapy with cis-platin based multi-agent regimen standard of care

- AUA: Strong Recommendation; Evidence Level: Grade B
- M-VAC/CMV only regimens tested in Phase III trials
- Common use of GC based on patients with metastatic disease and has not been evaluated in Phase III neoadjuvant trials
EORTC Adjuvant M-VAC

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

Fig. 2  Pooled hazard ratios across all nine studies by chemotherapy type CI = confidence interval; ES = effect size.

945 patients in 9 trials

HR 0.77 - 23% relative reduction in Death

• AUA: Patients with RC path pT3/T4 and/or N+ who have not received cisplatin-based NAC should be offered adjuvant cisplatin-based chemotherapy. (Moderate Recommendation; Evidence Level: Grade C)

• EAU and ASCO: Data are not convincing enough to give an unequivocal recommendation for the use of immediate adjuvant chemotherapy as compared to chemotherapy at the time of relapse (1A)

• NCCN: Consider if pT3-4, Tany N+, if no NAC given (2B)
• RISC database; 2005-2012; >pT2; 28 centers
  – NAC cT2, cN0, M0
  – NAC + RC or RC + AC pT2, any pN, M0
  – 656/1892 that underwent RC

DFS

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>NC</th>
<th>AC</th>
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</thead>
<tbody>
<tr>
<td>331</td>
<td>144</td>
<td>145</td>
</tr>
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<td>37</td>
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<td>28</td>
</tr>
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<td>3</td>
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OS

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<td>16</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>11</td>
</tr>
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</table>
VESPER - NCT01812369

- Phase III NAC or Adjuvant (Rouen)
- RC
- GC q3 weeks x 4 vs. HD M-VAC q 2weeks x 6
- Primary endpoint PFS at 3 years
- Powered to detect 10% improvement from 50% at 3 years with HD M-VAC
- 500 patients
• Currently one size fits all
• Prognostic biomarkers
• Predictive biomarkers
  – COXEN
  – DNA damage repair genes
  – Expression subtypes
• Precision medicine
COXEN prediction of treatment outcome in patients treated with neoadjuvant MVAC

Ref: Clin Can Res 2005;11(7): 2625
Tx: Neoadjuvant MVAC (N=45) + surgery or XRT
Outcome: Downstaging, Overall survival
SWOG S1314
COXEN Validation Neoadjuvant Chemotherapy Trial

Biomarker validation and Biomarker discovery

Activated July 1, 2014

Assessment
To characterize the relationship of MVAC- and GC-specific COXEN scores in terms of pT0 rate

Selection Criteria SWOG 8710 (T2-T4a N0M0, cisplatin eligible)

Tumour Sample TURBT

Randomize to chemo n=184

Randomization

Gem-Cis

DD-MVAC

Cystectomy Pathology

Collection
Tissue, blood, urine

Molecular Analysis
Gene expression
Sequencing
microRNA
SNP

Collection
Tissue (>P0), blood, urine

Molecular Analysis
Gene expression
Sequencing
microRNA
SNP

Tumor Sample TURBT

Collection
Tissue, blood, urine

Molecular Analysis
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microRNA
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Collection
Tissue (>P0), blood, urine

Molecular Analysis
Gene expression
Sequencing
microRNA
SNP

 activated July 1, 2014
DNA Damage Repair Pathway
Alterations Predict NAC Response

Van Allen et al, Cancer Discovery 4:1140, 2014

Iyer, et al JCO 36:1949-1956, 2018
ATM, FANC, RB-1 and NAC Response
A031701: A phase II study of dose-dense Gemcitabine plus Cisplatin in patients with muscle-invasive bladder cancer with bladder preservation for those patients whose tumors harbor deleterious DNA damage response (DDR) gene alterations

Modified DDR gene panel:
- ERCC2
- ERCC5
- BRCA1
- BRCA2
- RAD51C
- ATR
- RECQL4
- ATM
- FANCC

Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study.

246 patients screened
59 patients
187 patients

Courtesy Gopa Iyer
Blocking PGE$_2$–induced tumour repopulation abrogates bladder cancer chemoresistance

Antonina V. Kurtova$^{1,2}$, Jing Xiao$^3$, Qianxing Mo$^3$, Senthil Pazhanisamy$^4$, Ross Krasnow$^4$, Seth P. Lerner$^4$, Fengju Chen$^3$, Terrence T. Roh$^{1,5}$, Erica Lay$^4$, Philip Levy Ho$^6$ & Keith Syson Chan$^{1,2,3,4}$

Celecoxib with Chemotherapy in Localized, Muscle Invasive Bladder cancer (BLAST)

Tx: GC x 4 cycles + Celecoxib 100mg qd

Primary aims:

1) mRNA expression in pre- and post- chemotherapy specimens
2) Toxicity

**Future Treatment Paradigm for MIBC (?)**

**TCGA (n=412)**

**Luminal**
- KRT20+, GATA3+, FOXA1+

**Basal/Squamous**
- KRT5,6,14+, GATA3-, FOXA1-

**Neuronal**
- FGFR3 mut, fusion, amp
- Papillary histology
- SHH+
- Low CIS

**Luminal-papillary**
- Low risk
- NAC*
- FGFR3 inhibitors

**Luminal-infiltrated**
- Low purity
- EMT markers (TWIST1, ZEB1)
- miR-200 family
- Medium CD274 (PD-L1), CTLA-4
- Myofibroblast markers
  - 'p53-like'

**Luminal**
- UPKs
  - KRT20
  - SNX31

**Basal/Squamous**
- Female
- Squamous differentiation
- Basal keratin markers
- High CD274 (PD-L1), CTLA4
- Immune infiltrates

**Neuronal**
- SOX2
- DLX6
- MSI1
- PLEKHG4B
- E2F3/SOX4 amp
- High cell cycle

**Targeted therapy?**
- Anti-PD-L1, PD-1, CTLA-4

**Anti-PD-L1, PD-1, CTLA-4**
- Cisplatin-based NAC

**Cisplatin-based NAC**
- Low response rate

**Low risk response based on preliminary data (Seiler et al. 2017)**

**Etoposide/Cisplatin NAC**

* Cell, submitted
Retrospective Data: NAC Improves survival for Basal tumors (independent of Path at RC)

Seiler et al, EU 2017
Summary

• Level I evidence and guidelines support NAC in patients with T2-T4aNxM0 urothelial bladder cancer
• No high level evidence supporting Adjuvant chemotherapy
  – Up to 30% of patients may not be eligible after RC
• Current paradigm is a “one size fits all”
• Clinical trials testing predictive biomarkers
• Expression subtypes may stratify treatment approach but require validation