UROTHELIAL CELL CANCER

Indications and regimens for neoadjuvant systemic treatment

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LEARNING OBJECTIVES

- To understand the additional value of neoadjuvant systemic treatment for patients with urothelial cell cancer (UCC)
- To determine the optimal treatment regimen for individual patients
- To select patients with UCC for neoadjuvant systemic treatment
- To be aware of future developments
Neoadjuvant systemic treatment for patients with UCC:

- Why?
- Which?
- When?
- What’s next?
In UCC, neoadjuvant treatment...

- is administered for advanced disease
- is administered prior to the main therapy (i.e. surgery)
- has the potential to downstage the tumour (‘induction therapy’)
- can induce a pathological complete response
- has the potential to reduce tumour-associated symptoms (e.g. pain, haematuria)
- has the potential to facilitate surgery
- has the potential to target (micro)metastatic disease
- has the potential to improve progression-free and overall survival
- has curative intention in combination with local therapy (i.e. surgery)
UCC is a transitional cell cancer of the urinary tract including the bladder, ureter, urethra, and urachus.

- Tumours of the urinary bladder account for 90–95% of UCC\(^1\), whereas upper urinary tract UCCs account for 5–10%\(^2\).

- Literature on neoadjuvant systemic treatment for UCC not originating from the bladder is very limited\(^3,4\).

- The current ESMO E- Learning is therefore focused on bladder UCC.
NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHY?
Radical cystectomy with extended lymphadenectomy is the standard treatment of muscle-invasive bladder cancer (MIBC)\textsuperscript{1,2}

To improve patient outcome neoadjuvant chemotherapy (NAC) has been added to surgery\textsuperscript{3-5}

Bladder preserving strategies for MIBC can be considered when:

- A patient is medically unfit for surgery
- A patient prefers bladder preservation (with the option of a radical cystectomy as salvage therapy)

Bladder preserving strategies include transurethral resection of the bladder tumour (TURBT), radiotherapy, chemotherapy, or a combination of these.
Meta-analysis\textsuperscript{1,2} to evaluate the effect of NAC on overall survival (OS):

- 3005 patients from 11 randomised clinical trials were included
- Patients had clinical stage cT2-T4a MIBC
- Patients were treated with definitive treatment +/- NAC
- Local definitive treatment consisted of surgery, radiotherapy or both

**Platinum-based combination chemotherapy had a significant benefit on OS:**
- Hazard ratio (HR) 0.86 (95% CI 0.77 to 0.95, \(p = 0.003\))
- 14\% reduction in the risk of death
- 5\% absolute benefit at 5 years (OS increased from 45\% to 50\%)
- Effect was irrespective of the type of local treatment

\textsuperscript{1.} Advanced Bladder Cancer Meta-analysis Collaboration, Cochrane Database Syst Rev 2005; \textsuperscript{2.} Eur Urol 2005.
RATIONALE: SURVIVAL (OS)

Meta-analysis\textsuperscript{1,2} of overall survival (OS) with platinum-based combination vs. control

MORE BENEFIT TO BE EXPECTED?

Compared to the published meta-analyses, the survival is expected to be better in current practice, because of:

1. Optimised cisplatin-based chemotherapy schedules
2. Improved surgery with extended lymphadenectomy
3. Improved radiation techniques with improved treatment planning
Meta-analysis\textsuperscript{1,2} to evaluate the effect of NAC on disease-free survival (DFS):

- 3005 patients from 11 randomised clinical trials were included
- Patients had clinical stage cT2-T4a MIBC
- Patients were treated with definitive treatment +/- NAC
- Local definitive treatment consisted of surgery, radiotherapy or both

Platinum-based combination chemotherapy also had a significant benefit on DFS:

- Hazard ratio (HR) 0.78 (95% CI 0.71–0.86, \( p<0.0001 \))
- 9% absolute improvement at 5 years

META-ANALYSIS

To evaluate the effect of NAC on tumour response:

- 886 patients from 13 clinical trials were included
- Patients had MIBC
- Patients were treated with NAC and radical cystectomy, without any postoperative treatment

\[ \text{RATIONALE: RESPONSE} \]

- Pathologic complete response (pCR; pT0N0M0 stage) was 28.6%
- Patients with pCR after NAC had a better overall and recurrence-free survival than patients without pCR:
  - Relative risk (RR) for overall survival = 0.45
  - RR for recurrence-free survival = 0.19

In clinical practice, the majority of patients with resectable UCC do not receive NAC at all. 

Reasons for withholding NAC include:

- Cisplatin-ineligibility
- Comorbidities
- Advanced age
- Potential toxicity
- Perception of modest benefit
- Potential harm from delayed radical cystectomy

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHY NOT ADJUVANT?
There is no high level evidence for adjuvant therapy, as randomised trials of adjuvant therapy are incomplete or underpowered.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Eligibility</th>
<th>Regimen</th>
<th>Total patients randomly assigned</th>
<th>Completed accrual</th>
<th>Improved survival</th>
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<tbody>
<tr>
<td>Bono</td>
<td>pT2-T4a</td>
<td>Cisplatin plus methotrexate</td>
<td>90</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Freiha</td>
<td>P3b-4, N0 or N+</td>
<td>CMV</td>
<td>55</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Otto</td>
<td>pT3</td>
<td>MVEC</td>
<td>108</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Skinner</td>
<td>pT3-4 or N+</td>
<td>Multiple cisplatin-based combinations</td>
<td>102</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Lehmann</td>
<td>PT3-4a and/or pN+</td>
<td>MVAC or MVEC</td>
<td>49</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Studer</td>
<td>Multifocal recurrent pT1 or pT2-T4a</td>
<td>Cisplatin</td>
<td>91</td>
<td>No†</td>
<td>No</td>
</tr>
<tr>
<td>Stadler</td>
<td>pT1/T2 N0M0</td>
<td>MVAC</td>
<td>114</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cognetti</td>
<td>pT2 grade 3, N0-2; pT3-4, N0-2, any grade; or pN1-2, any T, any grade</td>
<td>GC</td>
<td>194</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Paz-Ares</td>
<td>pT3-4 and/or pN+</td>
<td>PCG</td>
<td>142</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sternberg</td>
<td>pT3-4 and/or pN+</td>
<td>GC, MVAC, or DD-MVAC</td>
<td>284</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

CMV, cisplatin, methotrexate and vinblastine; DD-MVAC, dose-dense methotrexate, vinblastine, doxorubicin and cisplatin; GC, gemcitabine plus cisplatin; MIBC, muscle-invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; MVEC, methotrexate, vinblastine, epirubicin and cisplatin; PCG, paclitaxel, cisplatin and gemcitabine.

*Stopped early because interim analysis favoured adjuvant chemotherapy.
†Stopped early because interim analysis favoured control arm of no adjuvant chemotherapy.

Meta-analysis to evaluate the effect of adjuvant therapy on survival:\(^1\):

- 945 patients from 9 randomised trials were included

Adjuvant chemotherapy appeared to have a significant benefit on:

- Overall survival: HR of 0.77 (95% CI 0.59 - 0.99, \(p = 0.049\))
- Disease-free survival: HR 0.66 (95% CI 0.45 - 0.91, \(p = 0.014\))

- These results were confirmed by an updated meta-analysis\(^2\)

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There is insufficient evidence for routine use of adjuvant chemotherapy for MIBC, as randomised trials of adjuvant therapy are incomplete or underpowered\textsuperscript{1,2}

- It is likely that high-risk patients (e.g. extravesical disease) who have not received NAC, will benefit most from adjuvant chemotherapy\textsuperscript{2}

- In selected cases, adjuvant chemotherapy may be considered\textsuperscript{2}, however high-level evidence is lacking

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHICH?
There is only high-level evidence for NAC consisting of 4 cycles of cisplatin-based combinations, including\textsuperscript{1,2}:

- Accelerated M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin)
  OR
- Gemcitabine-cisplatin

Based on randomised clinical trials in advanced and metastatic UCC, overall and progression-free survival are similar for MVAC and gemcitabine-cisplatin, whereas gemcitabine-cisplatin is associated with less toxicity\textsuperscript{3}

GEMCITABINE-CISPLATIN

SCHEDULE:

- Gemcitabine 1,000 mg/m² during 30-60 minutes on Days 1, 8, and 15
- Cisplatin 70 mg/m² on Day 2
- In clinical practice, gemcitabine on Day 15 is frequently cancelled

High dose or accelerated M-VAC consists of a 2-weekly regimen with G-CSF¹

In advanced and metastatic UCC, high dose M-VAC was compared with classic M-VAC¹

As compared with classic M-VAC, high dose M-VAC shows improved¹:
- Response rate (64% vs. 50%)
- Progression-free survival (median 9.5 vs. 8.1 months)
- Overall survival (OS rate at 5 years 21.8% vs. 13.5%)

Therefore high dose M-VAC is preferred instead of classic M-VAC¹

HIGH DOSE M-VAC (2)

CARBOPLATIN-BASED OR NOT?

Carboplatin-based NAC is not considered standard of care for cisplatin-ineligible patients, because$^{1-3}$:

1. Studies are lacking to support this

2. Cisplatin is superior

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHEN?
HOW TO SELECT PATIENTS?

1. Tumour characteristics

2. Patients characteristics
Patients with cT2-T4aN0M0¹ MIBC are eligible for NAC

### Definition of TNM

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: “flat tumour”</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscle</td>
</tr>
<tr>
<td>pT2a</td>
<td>Tumour invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>pT2b</td>
<td>Tumour invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical tissue</td>
</tr>
<tr>
<td>pT3a</td>
<td>Microscopically</td>
</tr>
<tr>
<td>pT3b</td>
<td>Macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades prostate, uterus, vagina</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades pelvic wall, abdominal wall</td>
</tr>
</tbody>
</table>

Staging of disease should at least include the following:

- Biopsy-proven UCC (cystoscopy)
- Adequate abdominal imaging of local disease (CT or MRI)
- Local imaging before TURBT
- Additional imaging (i.e. CT of the chest) to exclude metastases in patients at high risk of metastases

Patient characteristics important for NAC selection include\textsuperscript{1,2}:

- Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1)

- Laboratory results including full blood count and renal function (e.g. risk of hydronephrosis!)

- Co-morbidity

Suggested algorithm for the perioperative therapy of muscle-invasive bladder cancer (MIBC). Cr Cl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed death-1; PD-L1, programmed death-ligand 1. (*) Trials evaluating combinations of cisplatin-based chemotherapy with biologic agents should be considered.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHAT’S NEXT?
Ongoing and future clinical trials may evaluate whether neoadjuvant systemic therapy in UCC can be improved by:

- Checkpoint inhibitors (e.g. anti-PD1, PDL1, CTLA4)\(^1\)
- Inhibitors of VEGF signaling (e.g. ramucirumab)\(^2\)
- FGFR3 inhibitors\(^3\)
- Other...\(^4,5\)

Clinical trials on the treatment of locally UCC will focus on:\n
- Organ preservation strategies
- Adjuvant (systemic) therapy +/- neoadjuvant systemic therapy
- The development of new systemic therapies
- Introduction of (neo)adjuvant therapy at earlier disease stages
- More personalised therapy with better selection of patients

1. ClinicalTrials.gov
MOLECULAR CHARACTERISATION

Luminal
KRT20+, GATA3+, FOXA1+

Luminal-papillary
FGFR3 mut, fusion, amp
Papillary histology
SHH+
Low CIS

Luminal-infiltrated
Low purity
EMT markers (TWIST1, ZEB1)
mR-200 family
Medium CD274 (PD-L1), CTLA-4
Myofibroblast markers
Wild type p53

Luminal
UPKs
KRT20
SNX31

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

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

Etoposide/Cisplatin NAC

* Low predicted likelihood of response, based on preliminary data
** Low response rate

CONCLUSIONS

- Based on the highest level of evidence, cisplatin-based NAC with subsequent radical cystectomy is the current standard of care for cT2-T4aN0M0 MIBC

- Cisplatin-based NAC needs to be considered for every patient with cT2-T4aN0M0 MIBC

- As the treatment options for patients with UCC are expanding, participation in clinical trials is recommended and should always be considered
THANK YOU!