Chemotherapy in MI Bladder Cancer: Is neoadjuvant always necessary before radical cystectomy?

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ESOU Chairman

Conflict of Interest Disclosure

I have the following potential conflicts of interest to report:

- Consultant and advisory role: Ipsen, Sanofi Pasteur, Roche, Astellas, Arquer, Janssen, Ceipheid, Astra-Zeneca, Coloplast, Bouchara-Recordati, Lilly

- ESOU chairman
- Member of the EAU- guidelines panel NMIBC
- Head of the French association- guidelines panel Bladder Cancer
- I am a urologist, not an oncologist…
France 68 millions inhabitants/ Largest country in Europe (in size)

Around Paris = 13 millions inhabitants/

GPD (gross domestic product)
## Staging and survival MIBC

<table>
<thead>
<tr>
<th>Staging Stage</th>
<th>Description</th>
<th>Survival at 5 years</th>
<th>Positive LDN</th>
<th>Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2. Muscle</td>
<td>a) Superficial</td>
<td>75 %</td>
<td>15 %</td>
<td>3-6 %</td>
</tr>
<tr>
<td></td>
<td>b) Deep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT3. Perivesical fat</td>
<td>a) Microscopic</td>
<td>26-59 %</td>
<td>30-40 %</td>
<td>15-20 %</td>
</tr>
<tr>
<td></td>
<td>b) Macroscopic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT4</td>
<td>a) Invasion of prostate, uterus or vagina</td>
<td>7-30 %</td>
<td>40-60 %</td>
<td>15-30 %</td>
</tr>
<tr>
<td></td>
<td>b) Invasion of pelvic floor or abdominal wall</td>
<td></td>
<td></td>
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</tbody>
</table>
Recipe to cure muscle invasive bladder cancer?

Is there a « so-called » perfect cystectomy?

WHY SHOULD WE ADD CHEMOTHERAPY?
Rationale for Peri-operative Chemotherapy

• Deaths are generally not local events → patients die as a result of metastatic disease
• Local interventions will not deal with micrometastases
• Multi-agent chemotherapy can cure some patients with metastatic BCa
  → Systemic therapy could eradicate micrometastatic disease
  → Improve cure rates

Rationale for Neo-adjuvant Therapy

• Give systemic therapy when pelvic blood supply is intact
• Patients more fit - better able to tolerate chemotherapy
• In vivo chemo-sensitivity trial
• Deal with micrometastatic disease immediately
• Might facilitate surgery by decreasing tumor mass
• RC → complications → delay/prevention of adjuvant therapy
• Patients commonly refuse adjuvant therapy after RC
There is a man around his bladder: symptom control whilst respecting patients co-morbidities: a ‘Tailor’-made treatment.

Length of time

Review - Bladder Cancer

Delay in the Surgical Treatment of Bladder Cancer and Review of the Literature

[Graph showing time (months) for different types of bladder cancer cases]
Outcomes after MIBC

- Treatment decision
- Neoadjuvant Chemotherapy
- Quality of the surgery

Patients with Muscle Invasive Bladder Cancer → Patient decides on surgical intervention → Patient receives surgery → Outcomes for the patient

Neo adjuvant chemotherapy in MIBC: let’s be clear

• If curative, the purpose is not to downstage the MIBC tumor (example: T3N+ becoming a T2N0)

• This concept was not designed to make surgically extirpable a tumor which was not likely to be removed initially

• INDUCTION CHEMO. IS NOT NEO ADJUVANT CHEMO.
Chemotherapy

- Systemic cisplatin combination chemotherapy is the only current modality that has been shown to improve survival in phase 3 trials (grade A).
- MVAC combination was accepted in 1985 as an effective therapy in metastatic urothelial tumor.
- MVAC = methotrexate, vinblastine, doxorubicin and cisplatin (high-density or accelerated / shorter / add GCSF).
- 1 cycle of MVAC is either given over 2 weeks (14 days) or 4 weeks (28 days - accelerated MVAC).
- 3 to 6 cycles of MVAC.

WHAT ABOUT EAU GUIDELINES?

Guidelines EAU

Radical cystectomy is the gold standard for the management of muscle invasive bladder cancer.

Neoadjuvant cisplatin-containing combination chemotherapy should be offered in muscle-invasive BCa, irrespective of further treatment (grade A).

<table>
<thead>
<tr>
<th>Situation</th>
<th>Patients</th>
<th>Grade</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td>PS ≥1 et Clairance créat ≥ 60 ml/min</td>
<td>MVAC ou HD-MVAC</td>
<td>GC</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>PS ≥1 ou Clairance créat &lt; 60 ml/min</td>
<td>Pas de CTN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>PS ≥1 et Clairance créat ≥ 60 ml/min</td>
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<td></td>
</tr>
</tbody>
</table>
Neo-adjuvant chemotherapy

- not new concept (2003!)
- high level of evidence
- gain in survival is modest but undeniable (5%)

Neo adjuvant chemo.: OS BENEFIT

<table>
<thead>
<tr>
<th>Analysis</th>
<th>3 years</th>
<th>7 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 % vs 55.5 %</td>
<td>37 % vs 43 %</td>
<td>30 vs 36%</td>
</tr>
</tbody>
</table>

HR : 0.84 ; IC 95%, 0.72-0.99 ; p = 0.037

J Clin Oncol Apr 18, 2011
DATA IN FAVOR OF NEO ADJUVANT CHEMO

Meta-analysis

- 10 randomized trials
- 2688 patients
- decrease risk of death = 14%
- Benefit OS = 5%
- $p = 0.003$

CURRENT PRACTICE: UNDERUSE

In 2007 USA (National Cancer database) : only 11,6% eligible patients underwent a neo or adjuvant chemo !!

MANDATORY TUMOUR BOARD DISCUSSION
Histological variants

TURBT pathological assessment is usually not enough!

Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer


Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
Supported by the Sidney Kimmel Center for Prostate and Urologic Cancers.

- Data from this study suggest that patients with micropapillary bladder cancer have a similar rate of response to neoadjuvant chemotherapy to that of patients with urothelial carcinoma. If these patients have pT0 disease, their survival is significantly improved at 2 years.
PERI OPERATIVE Chemotherapy

Why should I do it?
NEO ADJUVANT:
- if well explained, well accepted
- Need for a perfect organization with oncologist (delay between end of chemo and procedure)
- Better acceptance of cystectomy from the patient (psychological impact)
- Criteria of response on imaging (CT) – impossible after surgery….

Who should get neoadjuvant chemotherapy in 2019?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>- T2-T4a /N0-N+/M0</td>
<td>- T1</td>
</tr>
<tr>
<td>- GFR suitable for cisplatinum</td>
<td>- M+</td>
</tr>
<tr>
<td>- Life expectancy &gt; 5 years</td>
<td>- Low GFR</td>
</tr>
<tr>
<td></td>
<td>- Poor Performance Status</td>
</tr>
<tr>
<td></td>
<td>« UNFIT » Patients</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy

Table 15 – Conclusions and recommendations for adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE</td>
</tr>
</tbody>
</table>

Table 7 – Recommendation for adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer adjuvant cisplatin-based combination chemotherapy to patients with pt3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.</td>
<td>C</td>
</tr>
</tbody>
</table>

GR = grade of recommendation.

Neo adjuvant chemotherapy in MI Bladder Cancer

STANDARD
Neo adjuvant Chemotherapy (cisplatin based) in suitable MIBC patients: OS improvement (5%) in several Phase III randomized trial and meta analysis

REAL LIFE
1. Only 40% of patients with major responses benefit from CNA
2. Neo adjuvant CT is non systematic in several countries

SOLUTION
Improve outcomes by identifying patients who are the most likely to respond to chemotherapy

ASCO GU 2018 – PC. Black; Session 4
Consensus on classification

Molecular subtypes

Luminal papillary = No chemo
- Low immune infiltration

Presented by: R. Seiler
Targeting PD-L1 and PD-1

Anti-PDL1

Programmed death-ligand 1

PD-L1 is expressed in urothelial bladder cancer > 20% cases


Current/future clinical trials in UC

NMIBC → MIBC → Metastatic UC

Low Grade → High Grade → neoadjuvant → Adjuvant → Refractory au BCG → Pembrolizumab/BCG

MPDL3280A → Nivolumab → Pembrolizumab

Fit

Maintenanc e

Platinum-resistant

1st line

2nd line

1. Pembrolizumab
2. MDPL3280A (Phase III)
3. MEDI4730
4. AMP-E14
5. MSB0010718C
6. MGA271

Metastatic UC

2. Nivolumab ± ipilimumab
3. Nivolumab/cabozantinib ± ipilimumab
4. Pembrolizumab/radiation
5. MDPL280A + Bevacizumab
6. MEDI4680 + MEDI4735

NMIBC → MIBC → Metastatic UC
Chemotherapy in M1 Bladder Cancer: Is neoadjuvant always necessary before radical cystectomy?

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