Debate of the day: SYSTEMIC CHEMOTHERAPY IS THE STANDARD FOR METASTATIC UROTHELIAL CANCER – NO

Camillo Porta
Department of Internal Medicine and Medical Therapeutics, University of Pavia & Division of Translational Oncology, I.R.C.C.S. Istituti Clinici Scientifici Maugeri, Pavia, Italy
## C. PORTA: DISCLOSURE OF INTEREST

<table>
<thead>
<tr>
<th>CONSULTANCY</th>
<th>SPEAKER</th>
<th>STEERING COMMITTEES</th>
<th>EXPERT TESTIMONY</th>
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WHERE CHEMO IS POSITIONED IN METASTATIC UROTHELIAL CANCER?

MORE IMPORTANTLY, WHICH CHEMO?

Metastatic 1L CDDP- ineligible

Approximately 50%¹

CDDP-unfit patients²:
- GFR < 60 ml/min
- PS ≥2
- ≥ grade 2 audiometric hearing loss
- ≥ 2 peripheral neuropathy
- NYHA Class III heart failure

WHAT CISPLATIN REALLY MEANS FOR PATIENTS?

CDDP-induced AKI: 20-40% of treated patients

CDDP-induced ototoxicity: 35-100% of treated patients

CDDP-induced peripheral neuropathy: 50-92%

CDDP-induced acute nausea: 8.5%

CDDP-induced delayed nausea: 47%

CDDP-induced high-grade acute emesis: 3%

CDDP-induced delayed emesis: 12-50%

WHICH RESULTS IN EXCHANGE FOR SUCH A HUGE TOXICITY?

<table>
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<tr>
<th>Disease setting</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic UC</th>
<th>≥ 2&lt;sup&gt;nd&lt;/sup&gt;-line Metastatic UC</th>
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<tr>
<td>Clinical setting</td>
<td>CDDP-fit (~50% of patients)</td>
<td>CDDP-unfit (~50% of patients)</td>
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<tr>
<td>Standard Tx</td>
<td>CDDP-based doublets</td>
<td>CBDCA-based doublets</td>
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<td>Expected results</td>
<td>ORR: ~36–72% mOS: ~13–16 mo</td>
<td>ORR: ~28–56% mOS: ~8–15 mo</td>
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5-year survival rate of mUC: ~15%
IF NOT CHEMOTHERAPY, WHAT ELSE? AND IN WHICH SETTING?

Immunotherapy

- Non-muscle invasive UC
- Muscle invasive UC
- Metastatic 1L CDDP-eligible
- Metastatic 1L CDDP-ineligible
- Maintenance
- 2L or beyond

Any T and N+
Any T, any N, M+

Approximately 50%¹

CDDP-unfit patients²:
- GFR < 60 ml/min
- PS ≥ 2
- ≥ grade 2 audiometric hearing loss
- ≥ 2 peripheral neuropathy
- NYHA Class III heart failure

2-cohorts, phase II study (310 pts), 2nd line, progression after platinum-based CT

Antitumor activity
ORR = 15%, CR = 5%, PR = 10%
mPFS = 2.1 mos, mOS = 7.9 mos
mPFS (imRECIST) = 4.0 mos
Higher ORR, PFS and OS for PD-L1+ pts


Phase II study (270 pts), 2nd line, PD after at least 1 platinum-based CT

Antitumor activity

ORR = 19.6%, CR = 2%, PR = 17%
mPFS = 2 mos, mOS = 8.7 mos

Higher ORR, PFS and OS for PD-L1+ pts


Phase I-II study (191 pts), 2nd line, PD after at least 1 platinum-based CT

Antitumor activity

ORR = 17.8.6%, CR = 3.7%, PR = 14.1%
mOS = 18.2 mos; better results for PD-L1+ pts

Expansion cohort of a phase I study (44 pts)
2nd line, PD after at least 1 previous CT line (CDDP-unfit patients were allowed)

**Antitumor activity**

ORR = 18.2%, CR = 11.4%, PR = 6.8%, SD = 34.1%

mOS = 13.7 mos; trend towards better results for PD-L1+ pts

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<th>Clinical Activity End Point</th>
<th>Avelumab (N = 44), No. (%)</th>
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<td>Confirmed best response, no. (%)</td>
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<tr>
<td>Complete response</td>
<td>5 (11.4)</td>
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<tr>
<td>Partial response</td>
<td>3 (6.8)</td>
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<tr>
<td>Stable disease</td>
<td>15 (34.1)</td>
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<tr>
<td>Progressive disease</td>
<td>15 (34.1)</td>
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<tr>
<td>Nonevaluable*</td>
<td>6 (13.6)</td>
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<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>18.2 (8.2 to 32.7)</td>
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<tr>
<td>Disease control rate, %</td>
<td>52.3</td>
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<tr>
<td>Median PFS, weeks (95% CI)</td>
<td>11.6 (6.1 to 17.4)</td>
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<td>PFS rate at 48 weeks, % (95% CI)</td>
<td>19.1 (8.5 to 32.8)</td>
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<tr>
<td>Median OS, months (95% CI)</td>
<td>13.7 (8.5 to ne)</td>
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<td>OS rate at 12 months, % (95% CI)</td>
<td>54.3 (37.9 to 68.1)</td>
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AVAILABLE PHASE III TRIALS IN 2ND-LINE (1)

Keynote 052 (Pembrolizumab)

Phase III study (334 pts) vs SOC (VFN, TXT or PTX)
2nd line, PD after 1 or 2 previous platinum-based CT

Events, n | HR (95% CI) | P
---|---|---
Pembro 155 | 0.73 (0.59-0.91) | 0.0022
Chemo 179 |

Median (95% CI)
10.3 mo (8.0-11.8)
7.4 mo (6.1-8.3)

OS, %

Time, months

CPS ≥10%

No. at risk

AVAILABLE PHASE III TRIALS IN 2ND-LINE (2)

**IMVigor 211 (Atezolizumab)**

Phase III study (931 pts) with hierarchical endpoints of Atezolizumab vs SOC (VFN, TXT or PTX) – 2nd line, PD at least 1 previous platinum-based CT

1. IC2/3 population

2. IC1/2/3 population

3. All comers

1\textsuperscript{ST} LINE TX OF CISPLATIN-UNFIT PATIENTS

IMVigor210 (Atezolizumab)

- Phase II study (374 pts), 1\textsuperscript{st} line, CDDP-unfit
- Antitumor activity
  - ORR = 24%
  - CR = 5%
  - PR = 19%
  - SD = 23%
- Combined score correla-ted to higher responses

Keynote 052 (Pembrolizumab)

- 2-cohorts, phase II study (123 pts), 1\textsuperscript{st} line, CDDP-unfit
- Antitumor activity
  - ORR = 23%, CR = 9%, PR = 14%
  - mPFS = 2.7 mos, mOS = 15.9 mos


WHAT ABOUT COMBINING CHEMO + I-O (BEYOND TOXICITY ISSUES)?

### Final PFS per ITT (arm A vs arm C)

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<th>Arm A</th>
<th>Arm C</th>
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<tr>
<td>Atezo + plat/gem</td>
<td>334 (74)</td>
<td>326 (82)</td>
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<tr>
<td>Placebo + plat/gem</td>
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- **PFS events, n (%)**: 334 (74) vs 326 (82)
- **Stratified HR (95% CI)**: 0.82 (0.70-0.96)
- **P = 0.007 (one-sided)**

TAKE HOME MESSAGES

- For years, platinum-based chemotherapy was the only available treatment for mUC, CDDP being superior as compared to CBDCA (differently from NSCLC).

- The activity of these combinations is relatively low, while tolerability is definitely poor, making half of mUC patients unsuitable for CDDP treatment.

- Despite somewhat controversial data, immunotherapy yields an efficacy which is superior, or at least equal, to that of chemotherapy, both in the second line, as well as in the first line, CDDP-unfit.

- Where available, immunotherapy should be regarded as the novel SoC in the above settings, chemotherapy no longer playing this role.

- Combinations of chemotherapy and immunotherapy warrant further investigations, with a particular eye on the balance between safety and efficacy.

THANK YOU VERY MUCH FOR YOUR KIND ATTENTION!!!

camillo.porta@unipv.it