NEOADJUVANT CHEMOTHERAPY IN CERVICAL CANCER

EVA MARÍA GOMEZ GARCIA MD
Medical Oncology

Cervix Cancer Education Symposium, January 2017, Mexico
Surgery +/- RT or QRT

1B2-IVA CONCOMITANT CHEMORADIOTherapy 6% 5 y (III-IV ???)

PALLIATIVE CHEMOTHERAPY +/- BEVACIZUMAB (toxicity)
Perez CA, Grigsby PW

Radiotherapy

Overall treatment period

Tumor size 4 cm

Lymph node enlargement

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Chin J Cancer Res 2016;28(2):221-227
AJCC Vision

The Transition from Population Based to a more "Personalized" Approach

- **AJCC/UICC TNM Stage** (Basic Classification)
  - TNM

- **AJCC Stage** (Advanced Clinical Relevance)
  - TNM
  - + Prognostic Factors

- **AJCC "Personalized"** (Advanced Clinical + Personalized Relevance)
  - TNM
  - + Prognostic Factors
  - + Risk Assessment Models
  - + Clinical Trial Stratification

Population Survival Outcomes

Personalized Survival Outcomes
1.- Increased peak concentration of cisplatin (CDDP) 89% vs 67% OS 5 y, distant failure 17% vs 23%, toxicity G3/4 39 vs 23%

2.- Surgery after chemo-radiotherapy. Residual disease 14-100%, surgical morbidity acceptable. No randomized trials.

3.- Adjuvant chemotherapy after chemo-radiotherapy. 2 trials Mito-C/5FU No sufficient evidence.

4.- Neoadjuvant chemotherapy before surgery or chemo-radiotherapy.

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RATIONALE FOR THE NEOADJUVANT CHEMOTHERAPY.

1.- Reducing the tumor size,
2.- Expediting the elimination of micrometastasis.
3.- Improving operability
4.-Surgical downstaging.
5. Is associated with fewer side effects than concurrent chemotherapy and radiotherapy.
## CHEMOTHERAPY AGENTS USED

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy regimen, doses</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoji et al., 2013</td>
<td>Carboplatin (AUC6), paclitaxel (175 mg/m²)/docetaxel (70 mg/m²)</td>
<td>2 (18 patients)</td>
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<td></td>
<td></td>
<td>3 (5 patients)</td>
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<tr>
<td>Shen et al., 2012</td>
<td>Cisplatin (20 mg/m² D1-4)/carboplatin (AUC5), paclitaxel (150 mg/m²)</td>
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<tr>
<td>Yamaguchi et al., 2012</td>
<td>Nedaplatin (80 mg/m²), irinotecan (60 mg/m² D1,8)</td>
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<tr>
<td>Pinheiro et al., 2011</td>
<td>Mitomycin C (10 mg/m²), methotrexate (300 mg/m² with folinic acid), bleomycin (15 mg/m² D1,8)</td>
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<tr>
<td>Vizza et al., 2011</td>
<td>Cisplatin (75 mg/m²), paclitaxel (175 mg/m²), ifosfamide (5 g/m², mesna)</td>
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<tr>
<td>Mossa et al., 2010</td>
<td>Cisplatin (50 mg/m²), vincristine (1 mg/m²), bleomycin (25 mg/m² D1,8)</td>
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<tr>
<td>Shoji et al., 2010</td>
<td>Cisplatin (70 mg/m²), irinotecan (70 mg/m² D1,8)</td>
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<tr>
<td>Cho et al., 2009</td>
<td>Cisplatin (75 mg/m²)/carboplatin (AUC5), paclitaxel (135 mg/m²)</td>
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<tr>
<td>Kokawa et al., 2007</td>
<td>Mitomycin-C (10 mg/m²), irinotecan (100 mg/m²) D1,8,15</td>
<td>2 (28 patients)</td>
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<td></td>
<td>Out of 28 days cycles</td>
<td>3 (7 patients)</td>
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<td>Sláma et al., 2007</td>
<td>Cisplatin (50 mg/m²), ifosfamide (5 g/m², mesna)</td>
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<tr>
<td>Eddy et al., 2007</td>
<td>Cisplatin, vincristine</td>
<td>3</td>
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<tr>
<td>Choi et al., 2006</td>
<td>Cisplatin (100 mg/m²), 5-fluorouracil (1000 mg/m²/day D2-5)</td>
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<tr>
<td>Cai et al., 2006</td>
<td>Cisplatin (100 mg/m²), 5-fluorouracil (1000 mg/m²/day D2-5)</td>
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<tr>
<td>Termrungranglert et al., 2005</td>
<td>Cisplatin (70 mg/m²), gemcitabine (1000 mg/m² D1,8)</td>
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<tr>
<td>Taneja et al., 2005</td>
<td>Cisplatin (50 mg/m²), bleomycin (15 mg/m² D1, 2), vincristine (1 mg/m²)</td>
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<tr>
<td>DeSouza et al., 2004</td>
<td>Cisplatin (60 mg/m²), methotrexate (300 mg/m² with folinic acid), bleomycin (30 mg/m² twice weekly)</td>
<td>3</td>
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</tbody>
</table>
## CHEMOTHERAPY AGENTS USED

<table>
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<th>Reference</th>
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<tbody>
<tr>
<td>Napolitano et al., 2003</td>
<td>Cisplatin (50 mg/m²), bleomycin (15 mg/m² D1, 2), vincristine (1 mg/m²)</td>
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<tr>
<td>D’Agostino et al., 2002</td>
<td>Cisplatin (100 mg/m²), epirubicin (100 mg/m²), paclitaxel (175 mg/m²)</td>
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<tr>
<td>Benedetti-Panici et al., 2002</td>
<td>Cisplatin (80 mg/m²), vincristine (1 mg/m²), bleomycin (25 mg/m² 3 days)</td>
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<tr>
<td>Duenas-Gonzalez et al., 2003</td>
<td>Carboplatin (AUC 6), paclitaxel (175 mg/m²)</td>
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<tr>
<td>Duenas-Gonzalez et al., 2002</td>
<td>Cisplatin (100 mg/m²), gemcitabine (1 mg/m² D1,8)</td>
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<tr>
<td>Costa et al., 2001</td>
<td>Cisplatin (40 mg/m²), epirubicin (30 mg/m²), etoposide (75 mg/m²), bleomycin (15 mg D1,2)</td>
</tr>
<tr>
<td>MacLeod et al., 2001</td>
<td>Cisplatin (50 mg/m²)/carboplatin (AUC5) based combination</td>
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<tr>
<td>Aoki et al., 2001</td>
<td>Cisplatin (60 mg/m²), vinblastine (4 mg/m² D1, 2), bleomycin (25 mg/m² 3 days)</td>
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<tr>
<td>Hwang et al., 2001</td>
<td>Cisplatin (50 mg/m²), vinblastine (6 mg/m²), bleomycin (25 mg/m² 3 days)</td>
</tr>
<tr>
<td>Chang et al., 2000</td>
<td>Cisplatin (50 mg/m²), vincristine (1 mg/m²), bleomycin (25 mg/m² for 3 days)</td>
</tr>
<tr>
<td>Zanetta et al., 1998</td>
<td>Cisplatin (50 mg/m²) (75 mg/m² in 10 patients), paclitaxel (175 mg/m²), ifosfamide (5 g/m², mesna)</td>
</tr>
<tr>
<td>Sardi et al., 1997</td>
<td>Cisplatin (50 mg/m²), vincristine (1 mg/m²), bleomycin (25 mg/m² D1-3)</td>
</tr>
<tr>
<td>Lacava et al., 1997</td>
<td>Vinrolbine (30 mg/m² weekly)</td>
</tr>
</tbody>
</table>
Neoadjuvant chemotherapy then surgery in locally advanced cervix cancer

Data was collected from 1760 patients enrolled in the above-mentioned studies (22 studies were phase II trials and 8 were phase III trials).

For response:
The ORR was 84%.
Trials that included platinum derivatives
ORR of 79%.
Studies that did not include platinum derivatives ORR of 80%,
P value was 0.07.
Down-staging 82%

Figure 1. Treatment response by stage. CR, complete remission; PR, partial remission; SD, stable disease; DP, disease progression.
Neoadjuvant chemotherapy then surgery or radiotherapy in locally advanced cervix cancer

- Stage IB2 to IIB, 43 patients
- Complete response 39%
- Partial response 51%
- Stable disease 9%
- Down-staging 72%

- Neoadjuvant chemotherapy then chemoradiotherapy phase II
- Respuesta completa 70% post-NACT
- 85% post-QRT.

Patients who received neoadjuvant chemotherapy, 90% of them underwent surgery,

The standard operation was radical hysterectomy with pelvic lymphadenectomy (type III, or IV).
5.6% underwent also para-aortic lymphadenectomy due to positive para-aortic lymph nodes.

Resection rate  OR, 1.55; 95% CI, 0.96–2.50; p = 0.07

JCOG 0102 N Katsumata, H Yoshikawa
Neoadjuvant chemotherapy plus QX vs QX or QRT

2010 The Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK, 1072 pacientes 1B1-III

PFS (HR, 0.76; 95% CI, 0.62–0.94; p = 0.01),

- STAGE 1B1-II
  - Progression-free survival 59% versus 13% p = 0.02
- Stage III
  - PFS : 41.9% vs 36.4%,
  - p = 0.29
Neoadjuvant chemo plus surgery vs radiotherapy

**Italy  stage 1B2-IIB**
Overall survival 5y
64.7% vs 18%  p = 0.005
Stage III
OS : 41.6% vs 36.7%,  p = 0.36;
Relative risk of OS QT + QX vs RT 0.63 (95% CI, 0.47–0.86).

Park, Dong Choon MD, PhD  Phase II
- OS 2 and 5 years  94 y 89%

Neoadjuvant chemotherapy plus QX vs QX or QRT

Retrospective
476 Patients  1B2-IIB
QT + Qx  vs QX
OS  1.813;  p = 0.0175
QT + Qx versus QRT
OS  HR, 3.157;  p < 0.0001

2010 The Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK, 1072 pacientes  1B1-III
- HR, 0.85; 95% CI, 0.67–1.07;  p = 0.17
• NACT + QX radical versus QX radical

• Phase III stage IB2, IIA2 y IIB

• N KATSUMATA

• Bleomicine, vincristine, mitomicin, cisplatin

• 134 patients

• Overall survival 70.0% NACT versus 74.4% surgery group \( P=0.85 \)

• High risk patients NACT 58% vs Qx 80% \( P=0.015 \)

• Many patients received radiotherapy

(JCOG 0102) N Katsumata, H Yoshikawa

• NACT + QX + ADYUVANCIA

OS 5 years 81% and PFS 70%, positive nodes 75% and negative nodes 88%.

Angioli, R Gynecol Oncol (2012).
NEOADJUVANT CHEMOTHERAPY

18 randomized trials  2074 patients

Interval between cycles
Cycles  <14 days  HR = 0.83, 95% CI = 0.69 to 1.00, p = 0.046
Cycles  >14 days  HR =1.25, 95% CI = 1.07 to 1.46, p = 0.005

Intensity of doses of cisplatin
> 25mg/m2 per week  HR = 0.91, 95% CI = 0.78 to 1.05, p = 0.20
< 25 mg/m2 per week  HR = 1.35, 95% CI = 1.11 to 1.14, p = 0.002

Histologies included squamous cell carcinoma, adenosquamous carcinoma, and/or, adenocarcinoma
Figure 1. Treatment response by stage. CR, complete remission; PR, partial remission; SD, stable disease; DP, disease progression.
TOXICITY

• QRT Toxicidad grado 3/4 20% durante la NACT (11% hematologica, 9% no-hematologica)
• Toxicidad grado ¾ 52% durante QRT concomitante (hematologica: 41%, no-hematologica: 22%)


The combination of chemotherapy followed by surgery is associated with fewer side effects than concurrent chemotherapy and radiotherapy.

The study of Tan and Zahra and Green et al. showed grade 3 and 4 late toxicity with a range of 18.3% to 22%, and reported urinary and/or intestinal complications.

Angioli, R Gynecol Oncol (2012).
Conclusiones:

MODERADO nivel de evidencia
Heterogeneidad en los estudios.
Brazos de comparacion no optimos
Esquemas de quimioterapia diversos.

Avances:
Ciclos cortos
Dosis densas.
Baja etapa
Mayor resecabilidad.
Similar toxicidad
**ESTUDIOS CORRIENDO**

**PHASE III**

**Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer (INTERLACE)**

**Control arm (CCRT alone)**
- XRT (40-50.4 Gy in 20-28 fractions) + BRT (minimal total EQD2 dose of 76-86 Gy)
- Concurrent CDDP 40 mg/m², weekly for 5 doses

**Experimental arm (Neoadjuvant CT + CCRT)**
- Neoadjuvant CT:
  - PTX: 80 mg/m² + CBDDA: AUC =2, weekly for 6 doses (day 1, 8, 15, 22, 29, and 36)
  - XRT (40-50.4 Gy in 20-28 fractions) + BRT (minimal total EQD2 dose of 76-86 Gy)
  - Concurrent CDDP 40 mg/m², weekly for 5 doses

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