Manejo terapéutico en pacientes con mCPRC con variantes histológicas indiferenciadas y agresivas

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Cáncer de Próstata Agresivo

Terminology Applied to Subsets of ‘Androgen Indifferent’ Prostate Cancers

- Small cell
- Neuroendocrine
- Aggressive Variant
- Atypical Intermediate
- Anaplastic

Modificado de Aparicio A. ASCOGU 2017
Criterios clínicos

1. Progresión con niveles bajos de PSA
2. Masas de partes blandas (> 5 cm) o tumor prostático voluminoso
3. Índice de Gleason ≥ 8
4. Metástasis viscerales exclusivas
5. Predominio de metástasis óseas lícticas
6. Componente de carcinoma de células pequeñas (puro o mixto)
7. PSA bajo: > 10 al diagnóstico de M1 o en CPRC de alto volumen (> 20 metástasis óseas)
8. Sensibilidad a castración inferior a 6 meses
9. Niveles elevados de LDH, CEA
10. Cromogranina A o GRP (gastrin released peptide) en tumor o elevados en suero

A Aparicio Clin Cancer Res 2013, Cancer Discovery 2011
Pattern and Distribution of Distant Metastases in Anaplastic Prostate Carcinoma: A Single-Institute Experience With 101 Patients.

Ganeshan D1, Aparicio AM2, Morani A1, Kundra V1.

Abstract

OBJECTIVE:
The aim of this study was to evaluate the sites and frequencies of distant metastases in patients with anaplastic prostate carcinoma and to correlate those findings with prostate-specific antigen (PSA) levels.

MATERIALS AND METHODS:
Patients with anaplastic prostate carcinoma (n = 101) underwent CT and bone scans before platinum-based chemotherapy. CT findings were retrospectively reviewed to identify the sites of metastases. CT findings were correlated with baseline PSA levels. The Wilcoxon rank sum test was used to correlate PSA levels between patients with metastases at osseous and nonosseous sites. The Wilcoxon rank sum test was also used to correlate the type of bone metastases (blastic vs lytic) and the PSA levels.

RESULTS:
Eighty-three of 101 patients (82%) had osseous metastases. PSA levels were significantly higher in patients with bone metastases than in patients without osseous metastases. However, 23 of the 83 patients (28%) with bone metastases had PSA levels in the normal range (i.e., < 4 ng/mL). The type of bone metastases (blastic vs lytic) did not show any statistically significant correlation to the PSA levels. Overall, 63 of 101 patients (62%) had nonosseous distant metastases at one or more sites, including the liver (n = 34), lung (n = 24), mediastinum (n = 31), pleura (n = 7), brain (n = 9), adrenal glands (n = 6), peritoneum (n = 4), and spleen (n = 1). PSA levels were not significantly elevated in patients with nonosseous distant metastases. Twenty-six of the 63 patients (41%) with nonosseous metastases had PSA levels in the normal range (< 4 ng/mL).

CONCLUSION:
Patients with the anaplastic clinical variant of prostate cancer have a high frequency of typical and atypical sites of metastases. Common sites of nonosseous distant metastases include the liver, lung, mediastinum, pleura, brain, and adrenal glands. PSA levels are unreliable and may be disproportionately low, despite the presence of multifocal large-volume metastases. CT of the chest, abdomen, and pelvis should be considered in routine staging and follow-up of patients with anaplastic prostate carcinoma regardless of their PSA levels.
Criterios patológicos

Carcinoma neuroendocrino puro (oat cell, cels grandes) AR-/NE+

Tumor mixto:
Carcinoma de células pequeñas AR-, NE +
y adenocarcinoma AR+, NE -

Carcinoma de células pequeñas, tipo células intermedias

Adenocarcinoma indiferenciado
Características moleculares

Modificado de Aparicio A
ASCO GU 2017
### Alteraciones moleculares

#### Table 1: Common Molecular Alterations Found in Small-Cell Prostate Carcinomas

<table>
<thead>
<tr>
<th>Category</th>
<th>Alteration</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Suppressor</strong></td>
<td><strong>RB1</strong> protein/allelic loss (85%-96%)[30,54,56]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TP53</strong> allelic loss/mutation (60%-100%)[54-56]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PTEN</strong> protein/allelic loss (29%-63%)[54,57]</td>
<td></td>
</tr>
<tr>
<td><strong>Prostate Luminal Epithelial Markers</strong></td>
<td><strong>AR</strong> protein loss (83%-100%)[18,19,21]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PSA</strong> protein loss (81%-100%)[10,16,18-21,23]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PSA1 s</strong> protein loss (72%)[19]</td>
<td></td>
</tr>
<tr>
<td><strong>Neuroendocrine Elements and Polypeptide Hormones</strong></td>
<td><strong>Chromogranin A and/or synaptophysin and/or CD56 protein expression</strong> (92%-100%)[18,19,21,34]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Bombesin</strong> protein expression (88%)[18]</td>
<td></td>
</tr>
<tr>
<td><strong>Neural Progenitor Transcription Factors</strong></td>
<td><strong>MYCN</strong> amplification (40%-83%)[13,57]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ASCL1</strong> protein expression[61]</td>
<td></td>
</tr>
<tr>
<td><strong>Cell Cycle/Mitosis Markers</strong></td>
<td><strong>AURKA</strong> amplification/protein expression* (40%-86%)[13,57]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>UBE2C</strong> protein expression (96%)[31]</td>
<td></td>
</tr>
<tr>
<td><strong>Genomic Alterations</strong></td>
<td><strong>Increased number of genomic amplifications and deletions</strong>[13,30,32]</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TMPRSS2:ERG</strong> gene rearrangements (46%-86%)[31,50,51,56-59]</td>
<td></td>
</tr>
</tbody>
</table>

*AURKA and MYCN amplification are concurrent in > 90% of reported cases.[13,57]

AR = androgen receptor; ASCL1 = achaete-scute homolog 1; PSA = prostate-specific antigen.

**Independencia de AR**

**Desdiferenciación Neuroendocrina**

**Proliferación**

A Aparicio. 2016
Combined Tumor Suppressor Defects Characterize Clinically Defined Aggressive Variant Prostate Cancers

Aparicio Clin Cancer Res 2016
Criterios clínicos-patológicos vs criterios moleculares

Alteraciones moleculares que definen el cáncer de próstata agresivo

Alterations (by IHC and/or genomic) in ≥ 2 of Tp53 / RB1 / PTEN

Modificado de Aparicio A
ASCOGU 2017
Alteraciones moleculares claves en la progresión neuroendocrina

Musquera Neoplasia 2013; Li, Cancer Cell 2016

N-Myc Drives Neuroendocrine Prostate Cancer Initiated from Human Prostate Epithelial Cells

HIGHLIGHTS
- N-Myc and AKT1 drive NEPC from human prostate epithelium
- Prostate epithelial cells can give rise to neuroendocrine and epithelial cancers
- N-Myc is essential for tumor maintenance in tumors initiated by N-Myc and AKT1
- Destabilization of N-Myc through Aurora A kinase inhibition induces tumor cell death
Incidencia

<table>
<thead>
<tr>
<th></th>
<th>Castration resistant</th>
<th>Newly diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell histology/gene expression</td>
<td>≈ 8%</td>
<td>&lt;1 %</td>
</tr>
<tr>
<td>Combined defects in ≥ 2 Tp53/RB1/PTEN</td>
<td>≈ 20%</td>
<td>≈10%</td>
</tr>
<tr>
<td>Primary resistance to androgen signaling inhibitors</td>
<td>≈ 20%</td>
<td>≈10%</td>
</tr>
</tbody>
</table>

Presented By Ana Aparicio at 2017
Genitourinary Cancers Symposium

Subclases patológicas asociadas a resistencia a abiraterona

Presented By Eric Small at 2015 ASCO Annual Meeting
Transdiferenciación neuroendocrina en cáncer de próstata

Stéphane Terry1,2* and Himisha Beltran**
Frontiers in Oncol, 2014 (rev)
Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer

Himisha Belinna1,2,12, Davide Prandi6,13, Juan Miguel Mosquera1,6, Matteo Benelli5, Loredana Pucci1, Joanna Cruta1, Clarisse Marotez4, Eugenia Giannopoulou8, Balabhadrapatruni V S K Chakravarthi9, Sooryanarayana Varanibelli9, Scott A Torin1, David M Nuss22, Scott T Tagawa1,9, Tluster M Van Allen2,10, Olivier Element6, Andreas Shomer15,21, Louis A Garraway8,9,12,14, Mark A Rubin13,5,14, & Francesco Damiani4,11,14

a. Linear progression
b. Independent from primary
c. Divergent from CRPC AD3C

2016
Tp53/RB1 (and PTEN) Loss Promote Lineage Plasticity and ‘Androgen indifference’

Presented By Ana Aparicio at 2017 Genitourinary Cancers Symposium
Quimioterapia en cáncer de próstata agresivo

| Table 2: Commonly Used Chemotherapy Combinations for the Treatment of Small-Cell Prostate Carcinomas*14,35,37,67-69 |
|-------------|-----------------|-----------------|--------------------|
| Cisplatin   | 25 mg/m²        | QD on days 1–3  | 21 days            |
| Etoposide   | 120 mg/m²       | QD on days 1–3  | 21 days            |
| Carboplatin | AUC 5           | Day 1           | 21 days            |
| Etoposide   | 100 mg/m²       | QD on days 1–3  | 21 days            |
| Carboplatin | AUC 5           | Day 1           | 21 days            |
| Docetaxel   | 75 mg/m²        | Day 1           | 21 days            |
| Cyclophosphamide | 1,000 mg/m² | Day 1 | 21 days |
| Adriamycin  | 40 mg/m²        | Day 1           | 21 days            |
| Vincristine | 2 mg            | Day 1           | 21 days            |

*Several variations of these chemotherapy doses and schedules have been published but are not listed here. AUC = area under the curve.
Quimioterapia en cáncer de próstata agresivo

El perfil clínico precide respuesta a la quimioterapia
Aggressive Variant Prostate Cancer: Clinical Criteria Predict for Chemotherapy Responsiveness

PCCTC (MDACC/UCSF)

Response to 1st Line Carboplatin & Docetaxel

Randomized Phase 2 Study Schema

Goal 160 pts

Randomization 1:1
Stratification:
ECOG (0,1 vs 2)
Prior Taxane 30%
  - Responder
  - Non-responder
AVPCa 60%

cabazitaxel 25 mg/m² q 3 wk
+ prednisone* for 10 cycles (n=80)

cabazitaxel 25 mg/m² q 3 wk
  carboplatin AUC 4
+ prednisone* for 10 cycles (n=80)

All patients receive Neulasta
  * 5 mg PO BID

Primary endpoint: PFS
Secondary endpoints: PSA and RECIST
  responses, bone specific alkaline
  phosphatase (BAP), and influence of
  AVPC criteria on response.

*Respondees:
1. Decrease in PSA >50% maintained for >6 weeks
2. PR or CR in lymph nodes and soft tissue
3. Have received ≥ 225mg/m2 (~3 cycles) of docetaxel.

Corn, ASCO, 2015
Figure 2. Median PFS. A, Overall population, B, Men with or without AVPC-C.

A

Overall Population

Progression-Free Survival Probability

\[ P = 0.006 \]

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
<th>Median PFS (Median Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
<td>76</td>
<td>71</td>
<td>6.29 (9.6, 8.88)</td>
</tr>
<tr>
<td>CAB/Carb</td>
<td>81</td>
<td>74</td>
<td>7.64 (6.17, 8.98)</td>
</tr>
</tbody>
</table>

B

Clinical Criteria

Progression-Free Survival Probability

\[ p = 0.017 \]

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment</th>
<th>N</th>
<th>Event</th>
<th>Median PFS (Median Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPC-C+</td>
<td>CAB</td>
<td>41</td>
<td>41</td>
<td>2.71 (2.85, 5.73)</td>
</tr>
<tr>
<td></td>
<td>CAB/Carb</td>
<td>43</td>
<td>43</td>
<td>2.64 (2.06, 3.64)</td>
</tr>
<tr>
<td>AVPC-C-</td>
<td>CAB</td>
<td>39</td>
<td>32</td>
<td>5.35 (4.48, 6.73)</td>
</tr>
<tr>
<td></td>
<td>CAB/Carb</td>
<td>38</td>
<td>31</td>
<td>7.81 (6.66, 8.93)</td>
</tr>
</tbody>
</table>

Figure 3. Median PFS. Men with or without AVPC-M in A, tumor biopsies and B, ctDNA.

A

Tumor Biopsies

Progression-Free Survival Probability

\[ p = 0.003 \]

\[ p = 0.014 \]

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment</th>
<th>N</th>
<th>Event</th>
<th>Median PFS (Median Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
<td>7</td>
<td>8</td>
<td></td>
<td>6.7 (2.9, 11.5)</td>
</tr>
<tr>
<td>CAB/Carb</td>
<td>10</td>
<td>12</td>
<td></td>
<td>8.4 (6.9, 11.5)</td>
</tr>
<tr>
<td>AVPC-C+</td>
<td>CAB</td>
<td>12</td>
<td>15</td>
<td>6.1 (2.9, 11.5)</td>
</tr>
<tr>
<td></td>
<td>CAB/Carb</td>
<td>22</td>
<td>21</td>
<td>5.4 (4.8, 6.3)</td>
</tr>
</tbody>
</table>

B

Preliminary ctDNA Analysis

Progression-Free Survival Probability

\[ p = 0.028 \]

\[ p = 0.056 \]

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment</th>
<th>N</th>
<th>Event</th>
<th>Median PFS (Median Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPC-C+</td>
<td>CAB</td>
<td>12</td>
<td>13</td>
<td>6.3 (3.6, 11.5)</td>
</tr>
<tr>
<td></td>
<td>CAB/Carb</td>
<td>17</td>
<td>17</td>
<td>5.3 (3.3, 7.3)</td>
</tr>
</tbody>
</table>

Aparicio A, ASCO, 2017
Tumor samples obtained ≤ 1 year of registration (n=73 from 64 patients) were subject to immunohistochemical (IHC) analysis for \textbf{Tp53} (M7001, Dako), \textbf{RB1} (OP66, EMD Millipore) and \textbf{PTEN} (6H2.1, Dako).
Sensibilidad a taxanos en CPRC

Jimenez N et al, enviado a ESMO 2017
The DynAMo Trial

n=265 CRPC

ABIRATERONE + APALUTAMIDE
8 weeks

8-week Serum Marker Decline

SATISFACTORY

+/- IPIлимумаб

UNSATISFACTORY

+ CABAZITAXEL & CARBOPLATIN

Presented By Ana Aparicio at 2017 Genitourinary Cancers Symposium
# Targeting neuroendocrine prostate cancer: molecular and clinical perspectives

**Panagiotis J. Vaskoutstegos** and Christos N. Papandreou

1. Department of Internal Medicine, Lutheran Medical Center, Brooklyn, NY USA
2. Department of Medical Oncology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

## Table 1: Targeted therapies in nPC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Molecular alteration</th>
<th>Pathway/pathway/process</th>
<th>Target</th>
<th>Agent</th>
<th>Result</th>
</tr>
</thead>
</table>
| [16, 18]  | TP53 mutation       | IL-8, CXCL8, sPDE2       | eNOS-Med1 | GATA-4 | Tumor regression in LNCaP mouse model, 
|           |                     |                         |        |       | Ph1 enhancing |
| [12, 69]  | MYD88 deletion      | FGFR-ERK-TRAF6           | Spindle disruption | Palbociclib, STI-571 | Enhanced mitotic and increased cell death in PCa, DU-145 cells |
| [14, 15, 59, 16] | PLK1 expression | AURKA, PLK1, Cyclin E2 | PI3K | BI 2536, BI 6728 | Decreased proliferation and autocrine potential of DU145, LNCaP PCa cells, reduced toxicity and efficacy in xenograft tumors, 
|           |                     |                         |        |       | PH1 ongoing |
| [15, 60]  | MYCN amplification  | MYCN, AURKA, p38, YIN/110c | ALKRA | Luteotrophin, dacarbazine | Increased aggressiveness in xenografts of DU145, LNCaP PCa cells, 
|           |                     |                         |        |       | Reduced tumorigenic potential of LNCaP and DU145, reduced 
|           |                     |                         |        |       | ALKRA protein, increased synaptophysin and 
|           |                     |                         |        |       | FLG expression in human PCa tumors with 
|           |                     |                         |        |       | deregulation of FLG and MYCN, growth inhibition of LNCaP and 
|           |                     |                         |        |       | DU145 PCa cell lines |
| [22, 22]  | PCDH4P overexpression | Wilms tumor suppressor  | PCDH4P | PCDH4P siRNA | Blocked RE differentiation of LNCaP sensitized human PCa tumors to 
|           |                     |                         |        |       | Androgens |
| [21, 39]  | P53 overexpression  | INK4a/AKtic | P53 | Vordermap | Immunoneutralization of P53 by the 
|           |                     |                         |        |       | bivalent vaccine and 
|           |                     |                         |        |       | immunotherapeutic effects in P53 in DU145 cells |
| [3, 4]    | TET overexpression  | NT-5R, RAB4, RAS-RAF | TET | 
|           |                     |                         |        |       | Suppression of expression of oncoproteins in patients with high-grade 
|           |                     |                         |        |       | disease and defined murine 
|           |                     |                         |        |       | xenograft models |
| [24, 19]  | MIF overexpression  | AKT/ERK, p53 | MIF | Ido-1 | Increased tumoral volumes and angiogenesis in patients with high-grade 
|           |                     |                         |        |       | disease and defined murine xenograft models |
| [24, 18]  | AKT activation      | Integrin-FAK, p53 | AKT | PF-05276710, 
|           |                     |                         |        |       | Depletion of AKT and AKT1 phosphatidylinositol 3 kinase activity. 
|           |                     |                         |        |       | Abrogation of 
|           |                     |                         |        |       | downstream signaling of DU145, LNCaP PCa cells, 
|           |                     |                         |        |       | TRAMPc cells |
| [51]      | Siah2 overexpression | I FF-1, FoxO2, 
|           |                     |                         |        |       | 
|           |                     |                         |        |       | Inhibition of autophagy and survival of DU145 cells |
| [3, 24]   | v-Kit amplification | MMP10, 64G, 64I | v-Kit | Imatinib, dasatinib, nilotinib, 
|           |                     |                         |        |       | Rosuvastatin, 
|           |                     |                         |        |       | Midostaurin, canarinarin |
| [3, 24]   | v-Kit amplification | MMP10, 64G, 64I | v-Kit | Imatinib, dasatinib, nilotinib, 
|           |                     |                         |        |       | Rosuvastatin, 
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|           |                     |                         |        |       | Midostaurin, canarinarin |
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|           |                     |                         |        |       | Rosuvastatin, 
|           |                     |                         |        |       | Midostaurin, canarinarin |
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|           |                     |                         |        |       | Inhibition of autophagy and survival of DU145 cells |
Differentially methylated genes and androgen receptor re-expression in small cell prostate carcinomas
Aurora Kinasas A (AURKA) como diana terapéutica

Familia de serina/treonina kinasas.
Regulan mitosis (sobretodo en proceso de segregación cromosómica) y meiosis
Isoformas A, B y C

AURKA controla proliferación,
Transición epitelio-mesénquima, metástasis,
capacidad autorenovadora de las cáncer stem cells

Tang, Oncotarget 2017
Inhibición de AURKA en el tratamiento de CPRC (alisertib)

Muerte celular

Inhibición de EMT

Degradación de NMyC

Niu et al. Frontiers in Oncology 2015
Inhibición de AURKA revierte el fenotipo neuroendocrino y frena la progresión tumoral

Beltran H, Cancer Discovery 2014
Inhibición de AURKA en el tratamiento de CPRC

Meulenbeld HJ, BJU Int 2013
Randomized phase II study of danusertib in pts with mCPRC after docetaxel failure

Lin, The Oncologist 2016
A Phase I/II Study of the Investigational Drug Alisertib in Combination With Abiraterone and Prednisone for Patients With Metastatic Castration-Resistant Prostate Cancer Progressing on Abiraterone

Beltran, ESMO 2016
A phase 2 study of the aurora kinase A inhibitor alisertib for patients with neuroendocrine prostate cancer
Beltran, ESMO 2016
A phase 2 study of the aurora kinase A inhibitor alisertib for patients with neuroendocrine prostate cancer

Methods
This is a multicenter Phase 2 study of alisertib 50mg BID x7d q21d for pts with metastatic prostate cancer and at least one: 1) NEPC morphology; 2) >50% NE marker IHC; 3) new liver metastases without PSA progression; 4) >3-5X serum NSE/CgA.

Results
59 pts (41 (70%) pathologic criteria, 26 (44%) clinical) were treated. Median age was 67 yrs (45-87), median PSA 1.13 ng/ml (0.01-514.2), and # of prior therapies 4 (15% enza/abi, 30% docetaxel, 29% platinum). Metastatic sites were bone (78%), lymph node (73%), lung (37%), and liver (61%). Of 56 evaluable pts, median PFS was 8.7 wks (8.0-10.4), 6 mo PFS 11.1% (16.3% for path NEPC; 5-31.6%), and median OS 38 wks (29.4-52.3). For those with scans SD/PR/CR at C3 (n = 17), median PFS was 20 wks (17-121) and 6 mo PFS was 35.8% (18.1% - 70.9%). Grade 3/4 toxicities identified in 5(9%) pts.
2 pts achieved exceptional response including complete resolution of liver metastases and a 3rd pt has stable disease at 39 mo follow-up. Correlation of molecular alterations (AURKA/MYCN, AR signaling, RB1/TP53) with clinicopathological features and characterization of exceptional responders including organoids will be presented.
Conclusiones

• Grupo clínicamente heterogéneo con evolución clínica agresiva
• Menor respuesta resistencia a la castración
• Sensibilidad a platino
• La caracterización molecular predice mejor la respuesta a la quimioterapia
• Es posible revertir algunas de las alteraciones moleculares asociadas al cáncer de próstata agresivo
Muchas gracias!!!