Intermittent Hormone Therapy: What Is Its Place in Clinical Practice?

Claude C. Schulman *
DISCLOSURE:

PI OF ICELAND STUDY (ASTELLAS)

FRIEND OF ISRAEL =

MEDICAL VOLUNTEER DURING 7 DAYS WAR IN 1967
Intermittent Androgen Deprivation (IAD): how and why?

- Cyclic therapy
  - On-treatment period
  - Off-treatment period

- IAD aims to
  - Minimise adverse events / improve quality of life (QoL)
  - Delay progression to hormone resistant prostate cancer
  - Reduce costs of care

Androgen Deprivation Therapy
Side effects

Body composition changes after androgen deprivation therapy
Metabolic Syndrome = The Deadly 4
Androgen resistance partly results from adaptive cell survival mechanisms activated by androgen withdrawal.

After initial ADT, remaining stem cells repopulate with androgen sensitive cells...

Providing androgens reintroduced before resistance occurred.

Scientific evidence

What’s the scientific evidence on IHT?

Phase II studies

Phase III studies
## Phase III studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>No of patients randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC/PR7</td>
<td>PSA relapse after RT</td>
<td>±300</td>
</tr>
<tr>
<td>EC 507</td>
<td>PSA relapse after RP</td>
<td>201</td>
</tr>
<tr>
<td>SEUG</td>
<td>Advanced PCa / M+</td>
<td>626</td>
</tr>
<tr>
<td>AP 17/95</td>
<td>Advanced PCa and M+</td>
<td>335</td>
</tr>
<tr>
<td>SWOG 9346</td>
<td>M+ PCa (PSA &gt; 5 ng/mL)</td>
<td>1,345</td>
</tr>
<tr>
<td>EC 210</td>
<td>M+ PCa (PSA &gt; 20 ng/mL)</td>
<td>194</td>
</tr>
<tr>
<td>ICELAND (Europe)</td>
<td>PSA relapse/ locally advanced</td>
<td>1131</td>
</tr>
</tbody>
</table>

Platinum Priority – Prostate Cancer
Editorial by Bertrand Tombal on pp. 1278–1280 of this issue

Intermittent Androgen Deprivation for Locally Advanced and Metastatic Prostate Cancer: Results from a Randomised Phase 3 Study of the South European Uroncological Group

Fernando E.C. Calais da Silva a,*, Aldo V. Bono b, Peter Whelan c, Maurizio Brausi d, Anton Marques Queimadelos e, Jose A. Portillo Martin f, Ziya Kirkali g, Fernando M.V. Calais da Silva h, Chris Robertson i

a Department of Urology, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
SEUG (2): no difference in overall survival

SEUG (3): time to progression slightly shorter with IAD.

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David I. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

ABSTRACT

BACKGROUND
Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

METHODS
Men with newly diagnosed, metastatic, hormone-sensitive prostate cancer, a per-
SWOG 9346 (2): a PSA ≤ 4 ng/mL after 7 months of CAD is a strong predictor of survival

N=1,345

Survival (months)

PSA after CAD-induction (ng/mL)

<0.2 ng/mL 0.2-4 ng/mL >4 ng/mL

75 months 44 months 13 months

Hussain M et al.  N Eng J Med
Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Juanita M. Crook, M.D., Christopher J. O’Callaghan, D.V.M., Ph.D., Graeme Duncan, M.D., David P. Dearnaley, M.D., Celestia S. Higano, M.D., Eric M. Horwitz, M.D., Eliot Frymire, M.A., Shawn Malone, M.D., Joseph Chin, M.D., Abdenour Nabid, M.D., Padraig Warde, M.B., Thomas Corbett, M.D., Steve Angyalfi, M.D., S. Larry Goldenberg, M.D., Mary K. Gospodorowicz, M.D., Fred Saad, M.D., John P. Logue, M.R.C.P., Emma Hall, Ph.D., Paul F. Schellhammer, M.D., Keyue Ding, Ph.D., and Laurence Klotz, M.D.

ABSTRACT

BACKGROUND
Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial.

From the British Columbia Cancer Agency, Kelowna (J.M.C., G.D.), NCIC Clinical Trials Group, Queen’s University, Kingston, ON (C.J.O., E.F., K.D.), Ottawa Cancer Centre, Ottawa (S.M.), London Health Sciences
Overall Survival (ITT)

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Median (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Androgen Deprivation (CAD)</td>
<td>9.1</td>
</tr>
<tr>
<td>Intermittent Androgen Suppression (IAS)</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Hazard Ratio 1.02 (95% CI = 0.86 – 1.21)

Test for non-inferiority of HR (IAS vs CAD) ≥ 1.25; p-value = 0.009

# At Risk

<table>
<thead>
<tr>
<th>Continuous</th>
<th>696</th>
<th>652</th>
<th>561</th>
<th>319</th>
<th>125</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>690</td>
<td>651</td>
<td>571</td>
<td>327</td>
<td>140</td>
<td>34</td>
</tr>
</tbody>
</table>
Disease-Specific Mortality (ITT)

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>7 year disease specific deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>15%</td>
</tr>
<tr>
<td>IAS</td>
<td>18%</td>
</tr>
</tbody>
</table>

Disease-Specific HR: 1.18 (95%CI = 0.90 - 1.55); p = 0.24
Prostate Cancer

Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND)

Claude Schulman\textsuperscript{a,\*}, Erik Cornel\textsuperscript{b}, Vsevolod Matveev\textsuperscript{c}, Teuvo L. Tammela\textsuperscript{d}, Jan Schraml\textsuperscript{e}, Henri Bensadoun\textsuperscript{f}, Wolfgang Warnack\textsuperscript{g}, Raj Persad\textsuperscript{h}, Marek Salagierski\textsuperscript{i}, Francisco Gómez Veiga\textsuperscript{j}, Edwina Baskin-Bey\textsuperscript{k}, Beatriz López\textsuperscript{k}, Bertrand Tombal\textsuperscript{l}
**Study design**

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Screening</th>
<th>Induction phase</th>
<th>Randomised phase</th>
<th>Long-term follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>7–14 d</td>
<td>6 mo</td>
<td>36 mo</td>
<td>18 mo</td>
</tr>
<tr>
<td>Days/months</td>
<td>~21–7</td>
<td>0–6</td>
<td>6–42</td>
<td>42–60</td>
</tr>
<tr>
<td>Visit(s)</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

- **Casodex® 50 mg qd for 1 mo**
- **Eligard® 22.5 mg 3-mo depot**
- **Eligard® 22.5 mg 3-mo depot**

**Randomisation**

- **Continuous ADT (CAD):**
  - Eligard® 22.5 mg 3-mo depot continuously

- **Intermittent ADT (IAD):**
  - Off-treatment phase followed by continuous ADT (Casodex® for 1-mo + Eligard®) if serum PSA >2.5 ng/mL. When serum PSA <1 ng/mL on 2 successive occasions medication was stopped

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation.

*a* Note: there is a discrepancy in the non-randomised group due to a patient who was not documented as a screening failure, whereas they should have been, based on the fact that one of the inclusion criteria was not met (locally advanced but Tumour Nodes Metastasis classification was missing); no leuprolide acetate was administered; b Population additionally included patients who were not randomised.
Study disposition

Screened
n = 1131

- Entered induction phase, n = 933
  - Analysed for safety, n = 932
  - Analysed for efficacy, n = 932

- Randomised, n = 701

Not eligible
n = 198

Discontinued/not randomised, n = 232
- Not fulfilling inclusion or exclusion criteria, n = 178 (76.9%)
- Adverse event, n = 5 (2.2%)
- Death, n = 6 (2.6%)
- Withdrawal of consent, n = 13 (5.6%)
- Subject lost to follow-up, n = 3 (1.3%)
- Protocol violation, n = 5 (2.2%)
- Worsening of disease, n = 3 (0.9%)
- Other, n = 22 (9.5%)

CAD
- Safety, n = 361
- Efficacy, n = 361

- CAD
  - Safety, n = 353
  - Efficacy, n = 352

- Withdrawals before follow-up (CAD)
  - Safety, n = 43
  - Efficacy, n = 43

- Entering the follow-up (CAD)
  - Safety, n = 310
  - Efficacy, n = 309

- Completing the follow-up (CAD)
  - Safety, n = 59
  - Efficacy, n = 59

IAA
- Safety, n = 340
- Efficacy, n = 340

- IAA
  - Safety, n = 337
  - Efficacy, n = 334

- Withdrawals before follow-up (IAA)
  - Safety, n = 45
  - Efficacy, n = 44

- Entering the follow-up (IAA)
  - Safety, n = 292
  - Efficacy, n = 290

- Completing the follow-up (IAA)
  - Safety, n = 42
  - Efficacy, n = 42
PSA levels at each visit

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen.
Testosterone levels at each visit

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation
Time to overall survival

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation
Time to PSA progression-free survival

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation
Summary

- This was a large, prospective, randomized trial of IAD and CAD conducted in the under-studied population of patients with non-metastatic locally-advanced or relapsing prostate cancer.

- There were no differences between IAD and CAD in relation to PSA progression, PSA progression-free survival, overall survival, mean PSA levels over time, or quality of life.

- A similar number of adverse events were observed in each group; the most common being hot flush and hypertension, and most were grade 1 (mild) or grade 2 (moderate).

- Given that IAD and CAD demonstrated comparable efficacy, tolerability and quality of life outcomes in patients with non-metastatic locally-advanced or relapsing prostate cancer, IAD may be a suitable treatment option for selected patients in this population.

- Results were seen in the context of a considerably lower number of injections in the IAD group than in the CAD group= Reduced Cost
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In Conclusion...

- IAD appears to have no negative impact compared to continuous HT in terms of overall survival or progression-free survival.

- IAD: Reduction of Cost

- IAD appears to have a Limited beneficial effect on QoL and side effects.

- It could NOT be demonstrated that IAD PROLONG time to CRPC.

- IAD may be a suitable treatment option for selected patients.
IAD: when to consider?

**PSA failure** (post RP / RxT) – **Non** Metastatic Disease
- Good PSA response (< 1.0 ng/mL) within 6 months of CAD initiation

**Metastatic:**
- Excellent PSA response (< 0.2 after 6 months)
- Asymptomatic
- **NO** large vertebral metastases or hydrenephrosis
- STOP IAD if rapid rise in PSA

**Do not consider IAD if:**
- Gleason score of 8 - 10
- High burden of metastatic disease or symptoms
- PSA > 50 ng/mL
Invited Commentary | 1 April 2016

Harms of Intermittent vs Continuous Androgen-Deprivation Therapy for Prostate Cancer

Saroj Nimaula, MBBS, MD, MSc1; Ian F. Tannock, MD, PhD2

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1CancerCare Manitoba, University of Manitoba, Winnipeg, Manitoba, Canada
2Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

Conclusions and Relevance
Contrary to our hypothesis that intermittent ADT would reduce long-term health-related events compared with continuous ADT, we found that older men assigned to I-ADT had no apparent reduction in bone, endocrine, or cognitive events and an increased incidence of ischemic and thrombotic events.
From: Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Metastatic Prostate Cancer

Intermittent Androgen Deprivation (IAD):

- **IAD concept aims to:**
  
  - Minimise adverse events / improve quality of life (QoL) = **limited / minimal**
  
  - Delay progression to hormone resistant prostate cancer: **NO**
  
  - Reduce costs ( **balance** cost of treatment / higher cost of Follow Up – Patients anxiety: **PSA = Patient Stress Amplifier !** )

IADT - Hypothesis

Androgen resistance partly results from adaptive cell survival mechanisms activated by androgen withdrawal.

After initial ADT, remaining stem cells repopulate with androgen sensitive cells...

Providing androgens reintroduced before resistance occurred.

Androgen Deprivation Followed by Acute Androgen Stimulation Selectively Sensitizes AR-Positive Prostate Cancer Cells to Ionizing Radiation.

Hedayati M¹, Haffner MC², Coulter JB¹, Raval RR¹, Zhang Y¹, Zhou H¹, Mian O¹, Knight EJ¹, Razavi N¹, Dalrymple S², Isaacs JT², Santos A¹, Hales R¹, Nelson WG³, Yegnasubramanian S⁴, DeWeese TL⁵.
BIPOLAR ANDROGEN THERAPY

- **Prostate.** 2010 Oct 1; 70(14):1600-7.

- Bipolar androgen therapy: the rationale for rapid cycling of supraphysiologic androgen/ablation in men with castration resistant prostate cancer.

- **Denmeade SR**¹, **Isaacs JT**.

- ¹The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA. denmesa@jhmi.edu
Sci Transl Med. 2015 Jan 7;7(269):269

Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study.


1The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. 
denmesa@jhmi.edu schweizer@uw.edu.

2The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.
BIPOLAR ANDROGEN THERAPY


- Bipolar androgen therapy for men with androgen ablation naïve prostate cancer: Results from the phase II BATMAN study.

- Schweizer MT¹, Wang H², Luber B², Nadal R², Spitz A², Rosen DM², Cao H², Antonarakis ES², Eisenberger MA², Carducci MA², Paller C², Denmeade SR².

¹Division of Oncology, Department of Medicine, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, Washington.

²Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland.
THE CONVENTIONAL VIEWS PROTECT US FROM THE PAINFUL JOB OF THINKING

J. K. GALBRAITH
Nobel Prize in Economics
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BIPOLAR ANDROGEN THERAPY

A

Growth inhibition (% of control)

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>10 mM R1881</th>
<th>10 μM bicalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNCaP/A-</td>
<td>90%</td>
<td>5%</td>
</tr>
<tr>
<td>VCaP/A-</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>LAPC-4/A-</td>
<td>70%</td>
<td>10%</td>
</tr>
</tbody>
</table>

B

R1881 concentration (M)

C

Control, DHT, ET, DHT/ET

D

Mean tumor volume (mm^3)

E

<table>
<thead>
<tr>
<th></th>
<th>Castrate</th>
<th>Castrate + T implants</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume (cm^3)</td>
<td>0.98 ± 0.19</td>
<td>0.32 ± 0.06</td>
<td>0.004</td>
</tr>
<tr>
<td>PSA/gram tumor</td>
<td>24.5 ± 8.0</td>
<td>95.5 ± 6.23</td>
<td>2 × 10^{-5}</td>
</tr>
<tr>
<td>Ki-67</td>
<td>83.0 ± 1.8%</td>
<td>81.1 ± 1.5%</td>
<td>0.4</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>0.51 ± 0.05</td>
<td>0.32 ± 0.07%</td>
<td>0.04</td>
</tr>
<tr>
<td>AR in nucleus</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>*</td>
</tr>
<tr>
<td>Cell death index</td>
<td>15 ± 2%</td>
<td>39 ± 3%</td>
<td>1 × 10^{-5}</td>
</tr>
<tr>
<td>AR in cytoplasm</td>
<td>7 ± 3%</td>
<td>77 ± 2%</td>
<td>**</td>
</tr>
</tbody>
</table>

F

No testosterone, Testosterone
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- Sci Transl Med. 2015 Jan 7;7(269):269
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