Intermittent Androgen Suppression - A standard of care or a good second choice?

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Uro-oncology Fellow

Olympic Medal Standings

<table>
<thead>
<tr>
<th>Country</th>
<th>Gold</th>
<th>Silver</th>
<th>Bronze</th>
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<td>USA</td>
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<td>New Zealand</td>
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Thank God for Rugby

ALL BLACKS vs Canada June 2007 64 to 13.

Objectives

- To summarize the historical background to IAS.
- To summarize the theoretical basis for IAS use.
- To summarize the data from phase II and III studies.
- To provide practical conclusions from the evidence available.
Historical Background

- Since Huggins et al demonstrated that castration resulted in regression of Prostate Cancer, hormonal manipulation has been the mainstay of treatment of those with significant disease in whom radical treatment is not possible.

Historical Background

- The first description of IAS for PCa was in the 1980s when Whitmore Jr et al first stopped Stilboestrol therapy in Adv PCa to alleviate side effects with minimal apparent detriment effect.

Why not just defer hormone therapy?

IAS is a feasible treatment option only if:

- Immediate therapy is better than deferred.
- Continuous androgen suppression has adverse effects.
- Adaptive (rather than clonal selection alone) mechanisms help mediate AI progression.
- Definable “on” and “off” trigger points.
- IAS non-inferior to continuous suppression.

Evidence Supporting Immediate Therapy

1. Xenografts: improved survival when castrated at low tumor volume (A So et al 2004).
2. Review of VACURG II: Decreased Ca-specific death rate (Byar et al 1977).
3. EORTC: Improved survival with adjuvant therapy post-radiotherapy (Bolla et al 2002).
4. MRC: Delayed time to progression and improved survival M2 CaP (BJU 1997).
5. ECOG: 2% vs 30% PCa mortality with immediate HT in N+ CaP (Messing NEJM 1999).
6. EPC Data - Casodex monotherapy trial (McLeod et al 2006).
7. EORTC 30853 Patients not suitable for curative intent showed significant improvement in overall survival. (Studer et al 2006).
Effects of Timing of Androgen Ablation on Time to AI Progression in Shionogi Tumor Model

Time to androgen-independent recurrence is directly proportional to tumor burden at time of castration

Immediate vs Delayed Androgen Ablation + RT

Radiotherapy Plus Adjuvant HT

- Bolla et al, EORTC.
- Phase III; Tx, high grade or T3-T4, n=415
- Randomized to RT alone vs RT + adj Zoladex X 3 yrs.

<table>
<thead>
<tr>
<th></th>
<th>cNED</th>
<th>Survival</th>
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<tr>
<td>RT alone</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>RT + HT</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td></td>
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</table>

ECOG 7887: Immediate HT vs Observation after RRP and PLND in N+ Patients.

- RCT RRP + PLND N+. Randomized to immediate vs delayed CAB.
- N= 98.
- Median 7 years follow up.

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>PCa deaths</th>
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<tr>
<td>Immediate</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Delayed</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
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**EPC Survival — Trial 25**

Localized vs Locally Advanced Patients

- Reduces radiographic and biochemical time to progression (predictable)
- OS adversely affected in Casodex arm in low risk CaP! (HR ~1.4)
- OS improved in Casodex arm in high risk CaP! (HR ~1.4)

Why not just defer hormone therapy?

- Systemic Review of 2167 patients treated in 4 RCTs conducted in 2002 treated with early vs deferred hormone therapy in the pre-PSA era demonstrated a benefit to early hormone treatment in terms of disease progression and a small but significant benefit in overall survival (5% at 10 years).


Why not just defer hormone therapy?

- Most recent EORTC 30853 analysis demonstrated a significant increase in overall survival with immediate treatment which the authors concluded was negated by the impaired quality of life seen with early hormone treatment\(^2\).

Ideal strategy would be one that starts Androgen Withdrawal Therapy early, but minimizes adverse effects.

IAS seems to be one such strategy!
Adverse Effects of ADT

- Short-term side effects
- Expense
- Long-term metabolic effects
  - decreased muscle mass
  - osteoporosis
  - anemia
  - lipid profile
  - immune surveillance
  - cardiovascular risk
  - cognition/mood

Balancing Benefits of Early Hormone Therapy

- Delayed progression
- Decreased local complications
- Improved survival
- Psychological benefits

- Short-term side effects
- Expense
- Long-term metabolic effects
  - decreased muscle mass
  - osteoporosis
  - anemia
  - lipid profile
  - immune surveillance
  - cardiovascular risk
  - cognition/mood

- IAS offers opportunity to improve quality of life
  - balances benefits of immediate androgen ablation
  - reduces treatment-related side effects and expense
Theoretical Basis for IAS

- Androgen resistance partly results from adaptive cell survival mechanisms activated by androgen withdrawal.
- If differentiating effects of androgens can modulate gene expression in tumor cells surviving androgen withdrawal, then progression to androgen independence may be delayed.

Mechanisms of Castrate Resistance
Noble 1977

“Although regression per se was not a prerequisite for autonomous change, the paradox was evident that progression towards autonomous growth was accelerated with a procedure expected to check tumor growth and was minimal with procedures that accelerated it.”
Animal Studies 1990s.

- Akakura et al used androgen dependent Shionogi mice to show that androgen independent stem cell clones seemed to adapt to low androgen environments.

Akakura K et al. Effects of intermittent androgen suppression on androgen dependent tumors. Cancer 993;71(9):2782-90.

Animal Studies 1990s.

- Sato et al then generated their own models of prostate cancer by inoculating LNCaP cells into SCID mice.

Sato et al., J Steroid Biochem Molec Biol 58:139, 1996
Animal Studies 1990s

- Sato et al
  - Castrate mice that received pulses of testosterone showed delayed onset of PSA rise. (26 vs 77 days).
- These results have been reproduced independently\(^3\).


Rationale: Testosterone is a Differentiating Agent
Have these results been replicated in Human Studies?

Principles of IAS

- The principal of IAS is that when a predetermined PSA nadir is reached hormone treatment is stopped.
- Treatment is restarted once the PSA rises to a predetermined level or when there is evidence of clinical progression.
Figure 1 The principle of IHT in a 72-year-old man with bone scan demonstrating metastatic disease and an initial PSA of 141 ng/ml.


IAS Protocols

- Several protocols have been used.
- Use either MAB or LHRH, Anti-androgen monotherapy.
- PSA cutoffs vary.
- Testosterone needs to be measured along with PSA to interpret accurately.
Clinical Studies - Phase II.

- There have been a number of phase II studies that have demonstrated the apparent safety of IAS.
- The larger of these studies were subjected to a meta-analysis in 2007.

Meta-analysis Summary

<table>
<thead>
<tr>
<th>Reference author</th>
<th>Origin</th>
<th>Type of disease</th>
<th>Type of treatment</th>
<th>PSA nadir for adequate response</th>
<th>Restart PSA</th>
<th>% off at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strum (29)</td>
<td>California, USA</td>
<td>L &amp; A</td>
<td>MAB</td>
<td>&lt;0.00</td>
<td>&gt;5</td>
<td>13</td>
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<tr>
<td>Youzef (20)</td>
<td>Michigan, USA</td>
<td>L, R &amp; A</td>
<td>MAB/mono</td>
<td>&lt;4</td>
<td>&gt;10</td>
<td>39</td>
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<tr>
<td>Malone (26)</td>
<td>Ottawa, Canada</td>
<td>L, R &amp; A</td>
<td>MAB/mono</td>
<td>&lt;4</td>
<td>&gt;10</td>
<td>20</td>
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<tr>
<td>Grosefield (22)</td>
<td>San Francisco, USA</td>
<td>L, R</td>
<td>MAB/mono</td>
<td>&lt;4 if no prev. Rx</td>
<td>&gt;10</td>
<td>36</td>
</tr>
<tr>
<td>De La Taille (23)</td>
<td>Perp, France</td>
<td>L, R &amp; A</td>
<td>MAB/mono</td>
<td>&lt;1 if prev Rx</td>
<td>&gt;0.5 post RT/RP</td>
<td>11</td>
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<tr>
<td>Goldemberg (24)</td>
<td>Vancouver, Canada</td>
<td>L, R &amp; A</td>
<td>MAB/mono</td>
<td>&lt;0.5 post RT/RP</td>
<td>&gt;4 post RT</td>
<td>17</td>
</tr>
<tr>
<td>Spy (28)</td>
<td>Perth, Australia</td>
<td>L, R &amp; A</td>
<td>MAB</td>
<td>Variable - all 9 months MAB</td>
<td>&gt;10</td>
<td>31</td>
</tr>
<tr>
<td>Pernich (27)</td>
<td>Paris, France</td>
<td>L, R &amp; A</td>
<td>MAB</td>
<td>&lt;4</td>
<td>&gt;20</td>
<td>40</td>
</tr>
<tr>
<td>Albrecht (21)</td>
<td>Europe</td>
<td>A</td>
<td>MAB</td>
<td>&lt;20 or &gt;20% Initial</td>
<td>&gt;20 or &gt;1.5 nadir</td>
<td>6 (at 1 year)</td>
</tr>
</tbody>
</table>

Length of Treatment & PSA Threshold for Restarting Treatment.


Principles of IAS based on Phase II Evidence.

- Approx 95% of patients can be expected to have a PSA response adequate to cease hormone therapy.
- This proportion decreases with each subsequent cycle.
- Patients who fail to reach an adequate nadir have poorest prognosis.
Phase II Studies

- The pooled data from these patients generated hypotheses to be tested in RCTs in terms of optimising medication type and treatment cycling parameters.

Phase III Studies

- Number of Phase III trials have been completed.
- 5 of these were included in Cochrane review in 2007.
  - Portuguese Southern European Cooperative Trial (Calais F et al Eur Urol 2002).
  - Belgium Trial (de Leval J et al Clinical Prostate Cancer 2002).
  - EUA TULP (Schasfoort E et al 2002).
  - Japanese Trial (Yamanaka H et al Prostate 2005).
  - Brazil Trial (Hering F Braz J Urol 2000).
Portuguese RCT

- RCT IAS vs Continuous in Loc Adv or Metastatic PCa.
- 1045 men registered 1999 to 2007:
  - PSA<10: 24%
  - PSA >20: 39%
  - Median PSA: 15.9
  - 90% T3; 13.5% Mets
- Treated with CPA and monthly LHRH for 3 months prior to randomization.
- 914 randomized to IAS (460) or CAD (454).
- Median followup 2 years (maximum 7 years).


Portuguese RCT

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>IAS</th>
<th>CAD</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Hot flushes</td>
<td>7%</td>
<td>23%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>10%</td>
<td>33%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headaches</td>
<td>5%</td>
<td>12%</td>
<td>&lt;0.0001</td>
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Sexual Activity (30% sexually active pre-registration)

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-random</th>
<th>6 mos post</th>
<th>12 mos post</th>
<th>24 mos post</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>24%</td>
<td>33%</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>20%</td>
<td>19%</td>
<td>8%</td>
</tr>
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</table>

p-values:
- p=0.67
- p=0.002
- p=0.06
- p=0.0001

Portuguese RCT

IAS patients: Time off therapy

- 40% remain off therapy 3.5 years after randomization.
- 20% began cycle 2 within 1 year off Rx.
- Median time off therapy:
  - PSA <1 at randomization: 174 weeks
  - PSA 1-4 at randomization: 100 weeks
  (p<0.05)


Cochrane Review 2007

- 5RCTs including 1382 patients.
- All the studies involved locally advanced PCa.
- All had relatively small populations and were of short duration.
- None evaluated disease-specific survival or metastatic disease. One evaluated biochemical outcomes.
**Cochrane Review 2007**

- Mainly reported on adverse outcomes and significantly lower impotence in the IAS group.
- Conclusion was that there was no evidence to support IAS over Continuous Hormone Therapy.

**Ongoing Phase III Trials**

- NCIC PR7
  - Biochemical failure following radiotherapy that are N0. N=1360. Outcome measures PSA kinetics and QoL.
Ongoing Phase III Trials

- SWOG 9346 (NCIC PR8)
  - Patients with newly diagnosed metastatic PCa. N=1500.
  - Induction phase with CAB (7 months).
  - Arm I - as above until progression.
  - Arm II - observe until evidence of rise in PSA or clinical progression. Repeat induction treatment.
  - QoL measured regularly.

Future Directions - Prolonging the Off Cycle Period.

- Use of 5-α-Reductase Inhibitors.
  - Retrospective data by Sholtz et al in 2006 showed using finasteride during the off cycle of IAS doubled the off treatment period and is hypothesis forming.
  - This lead to the initiation of a RCT (AVIAS - DUT 104923). Multicentre, double blinded study comparing 0.5mg dutasteride vs placebo daily in men receiving intermittent androgen ablation therapy for prostate cancer.
Conclusions for Clinical Practice

- There is good Phase II and Phase III evidence to suggest that IAS is non-inferior in terms of survival compared to Continuous Androgen Ablation.

Conclusions for Clinical Practice

Candidates for IAS?

- Serum PSA < 4 µg/L after 6 months of ADT.
- Stage N+ (M1 disease).
- Biochemical recurrences post-XRT or surgery.

- Consider life expectancy, risk factors, PSAdt.
Conclusions for Clinical Practice

When should therapy be re-started?

- M1, high pretreatment PSA - restart when PSA ~20.
- Post RT - PSA 6-10 or return to pretreatment levels.
- Post-RRP - PSA 1-4 or return to baseline.
  - Consider life expectancy, risk factors, PSAdt.

Conclusions for Clinical Practice

Duration of ‘on’ treatment cycle?

- 6 - 9 months.
Conclusions for Clinical Practice

- It seems logical and likely that there is a QoL benefit to IAS over CAA.
- Confirmation of this needs further Phase III data.

Conclusions for Clinical Practice

- Those patients who fail to reach a low nadir have poor outcome.
- In all of this we are relying on PSA as being a good surrogate of response.
Conclusions for Clinical Practice

- There is likely to be a significant economic benefit to IAS over CAA. Both in terms of reduced medication costs, but also treatment costs in terms of adverse effects of hormone therapies.

Conclusions for Clinical Practice

- We await the outcomes of the two big NCI trials.
Acknowledgements

- Dr Gleave
- Dr Goldenberg

For use of their personal slide collection.