

Prostate cancer

INTERMITTENT VS CONTINUOUS ANDROGEN SUPPRESSION

David Cuthbert, MD, FRCPC, Fellow, Department of Radiation Oncology, Princess Margaret Hospital and University of Toronto.
Padraig Warde, MB, MRCPI, FRCPC, Professor, Department of Radiation Oncology, Princess Margaret Hospital and University of Toronto; Deputy Head, Radiation Medicine Program, Princess Margaret Hospital, Toronto.

TRIAL SUMMARY: Quality of life benefits linked with intermittent androgen suppression

Crook J, Malone S, Duncan G et al. A phase III randomized trial of intermittent versus continuous androgen suppression for patients with PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/UK Intercontinental Trial Cruke/01/013). CARO 2011. Abstract 38.

Eligible patients for this study had a rising PSA >3 ng/mL post primary or salvage radiotherapy with or without up to 1 year of neoadjuvant or adjuvant androgen deprivation therapy (ADT) for localized prostate cancer. Intermittent androgen suppression (IAS) cycles were 8 months of treatment with prostate-specific antigen (PSA)-determined off-treatment periods. The primary endpoint was overall survival (OS).

Six hundred and ninety patients were randomized to IAS and 696 to continuous androgen deprivation (CAD). Mean age was 74.2 years and mean duration of followup was 6.9 years. Baseline factors were balanced. The IAS patients completed one to nine 8-month cycles (median=2), with no differences in adverse effects such as myocardial events.

COMMENTARY: After radical localized therapy for prostate cancer, >30% of patients will develop biochemical recurrence,¹ and ADT is the mainstay of treatment in this setting. The standard approach to ADT has been to continue therapy until death (even after the development of castrate-resistant disease) — often with profound life-changing side effects including fatigue, loss of libido, weight gain, anemia, cognitive effects, depression and hot flashes. There has been increasing interest in an intermittent treatment approach over the past 20 years, as a strategy to both prolong time to the development of androgen independence as well as improve the QoL of patients on treatment.

The rationale for suggesting that IAS might increase the time to development of castrate-resistant disease stems from preclinical studies of the LNCaP and Shionogi tumour models, which suggested a benefit to re-exposure to androgens after a period of androgen withdrawal.^{1,2} Multiple Phase II studies have demonstrated the safety and feasibility of IAS; patients spent approximately 40% of the time off treatment. They also experienced improvement in sexual function and quality of life during the off-treatment period.³⁻⁶

Prior to the current study, 2 Phase III studies examined IAS vs CAD with regards to time to progression to castrate-resistant disease.^{7,8} Leval et al reported on a study of 77 patients (75% with no clinical evidence of metastatic disease). With only a short median followup of 30 months, disease pro-

TABLE 1. Planned interim analysis results after 400 events in intermittent vs continuous androgen suppression arms

	IAS n=690	CAD n=696
Number of deaths	268	256
Median OS (years) HR=1.02, 95% CI: 0.86–1.21; p for noninferiority (HR IAS vs CAD) ≥1.25	8.8	9.1
Disease-related deaths	97	122
Disease-unrelated deaths	146	134

IAS=intermittent androgen suppression
OS=overall survival
CI=confidence interval

CAD=continuous androgen deprivation
HR=hazard ratio

Cross-sectional quality of life (QoL) analysis showed a range of benefits with IAS. Median OS was 8.8 vs 9.1 years on IAS vs CAD, respectively. Based on the planned interim analysis, the authors concluded that IAS is not inferior to CAD with respect to OS, but benefits were shown in QoL measures. Results of the interim analysis are presented in **Table 1**.

gression at 3 years was 7% in the intermittent arm vs 39% in the continuous arm.⁷ The South European Urological Group (SEUG) 904 study randomized 626 patients to IAS vs CAD. With a median followup of 51 months, there was no difference in time to disease progression.⁸ Although the study was not powered to properly assess this endpoint, OS was equivalent in the two treatment arms.

The National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) PR.7 trial is the first study to evaluate IAS vs CAD with OS as the primary endpoint. A total of 1386 patients, all of whom had no clinical evidence of metastatic disease (M0), were randomized to IAS or CAD. The trial design was a noninferiority study: IAD consisted of 8-month treatment cycles, with a minimum of 4 weeks of a nonsteroidal antiandrogen in addition to a luteinizing hormone-releasing hormone analog (LHRHa). Treatment was restarted with PSA >10 ng/mL, and CAD initiated with disease progression or if a rapidly rising PSA was noted. With a median followup of 6.9 years and 524 deaths, there was no difference in OS between the 2 study arms. Median OS was 8.8 years (IAS) vs 9.1 years (CAD). IAS patients completed a median of two 8-month cycles (range 1–9) and QoL analysis demonstrated improvement with this approach. This trial has clearly established IAS as the preferred treatment strategy for patients with biochemical relapse or locally advanced disease not amenable to local

therapy (in metastatic disease, the standard management remains CAD and the results of the NCIC CTG PR.8 study are awaited with interest).

This study has not addressed the issue of which patients would benefit from an intermittent therapy approach — the results of a companion translational study may shed light on this issue. Another highly clinically relevant issue to physicians in their everyday practice that remains unanswered is when ADT should be started in this group of patients. Newer hormonal agents, including abiraterone and MDV3100, are now coming on the market and it is unclear how they should be integrated with current approaches.

References

1. Bruchovsky N, Rennie PS, Coldman AJ et al. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. *Cancer Res* 1990;50:2275-82.
2. Akakura K, Bruchovsky N, Goldenberg SL et al. Effects of intermittent androgen suppression on androgen-dependent tumors: apoptosis and serum prostate-specific antigen. *Cancer* 1993;71:2782-90.
3. Shaw GL, Wilson P, Cuzick J et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. *BJU Int* 2007;99:1056-65.
4. Bouchot O, Lenormand L, Karam G et al. Intermittent androgen suppression in the treatment of metastatic prostate cancer. *Eur Urol* 2000; 38:543-9.
5. Goldenberg SL, Gleave ME, Taylor D, Bruchovsky N. Clinical experience with androgen suppression in prostate cancer: minimum of 3 years' follow-up. *Mol Urol* 1999;3:287-92.
6. Grossfeld GD, Small EJ, Carroll PR. Intermittent androgen deprivation for clinically localized prostate cancer: initial experience. *Urology* 1998;51:137-44.
7. de Leval J, Boca P, Yousef E et al. Intermittent versus continuous total androgen

IN BRIEF

Already known

- Androgen deprivation therapy is effective in patients with prostate cancer who relapse after primary treatment.
- Until now, the standard strategy has been continuous treatment until death.

What this study showed

- An intermittent approach to androgen deprivation therapy is safe and results in improved quality of life for patients when they are off treatment.

Next steps

- Further research is needed to determine which patients will benefit from this approach, when androgen deprivation therapy should be started in these patients, and the impact of new agents such as abiraterone and MDV1000.

- blockade in the treatment of patients with advanced hormone-naive prostate cancer: results of a prospective randomized multicenter trial. *Clin Prostate Cancer* 2002;1:163-171.
8. Calais da Silva FE, Bono AV, Whelan P et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Urooncological Group. *Eur Urol* 2009;55:1269-77.