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REVIEW ARTICLE

Androgen deprivation therapy in advanced prostate cancer: is intermittent therapy the new standard of care?

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ABSTRACT

Purpose

Intermittent androgen deprivation is increasingly used as an alternative to continuous life-long androgen deprivation therapy for men with advanced or recurrent prostate cancer.

Recent Findings

Two recent phase III trials have clarified the benefits of intermittent therapy. The Canadian-led PR.7 trial in men with nonmetastatic disease and prostate-specific antigen recurrence after definitive local therapy showed that intermittent therapy resulted in survival equivalent to that with continuous therapy, with significant improvements in quality of life. Patients on intermittent therapy experienced improved bone health, fewer metabolic and hematologic disturbances, fewer hot flashes, and improved sexual function.

In men with metastatic disease, the data are less clear. The long-awaited results of the Southwest Oncology Group 9346 trial, comparing intermittent with continuous therapy in metastatic disease, showed no difference in overall survival. *Post hoc* stratification analysis showed a worse outcome in patients with "minimal" metastatic disease, and no difference in those with widespread bone metastases. The significance of that observation is in dispute.

The present review also addresses practical issues in the use of intermittent therapy, including patient selection, follow-up, and therapy cycling.

Summary

The recent results of randomized clinical trials now establish that intermittent androgen deprivation therapy is an approach that should be considered the standard of care in most patients with nonmetastatic prostate cancer requiring hormonal therapy and in selected patients with metastatic disease.

Key Points

- Level I evidence supports the oncologic equivalence of intermittent compared with continuous androgen blockade in men with biochemical failure.
- Compared with continuous androgen deprivation, intermittent therapy demonstrates improved quality of life and fewer side effects.
- Patient selection for intermittent therapy is important to maintain good oncologic results.
- Monitoring of prostate-specific androgen response and duration of off-treatment intervals allow for stratification of patients by risk of progression.

KEY WORDS

Androgen deprivation therapy, prostate cancer, quality of life

1. INTRODUCTION

Androgen deprivation therapy (ADT) for prostate cancer was first described in 1941 by Huggins and Hodges. It is well known that Huggins received the Nobel Prize in Physiology or Medicine for that observation[1]. Remarkably, a second Nobel Prize in Physiology or Medicine was awarded for the discovery of ADT—to Andrew Schally for the luteinizing-hormone releasing-hormone (LHRH) agonists.

Androgen deprivation therapy remains one of the most effective palliative treatments for patients with prostate cancer. Since 1990, the LHRH agonists have large replaced surgical castration and diethylstilbestrol. The appeal of the agonists is their reversibility. Data on the adverse systemic effects of ADT have increasing emerged since the early 2000s. Androgen deprivation therapy is associated with multiple side effects, including hot flushes, decreased energy, loss of libido, erectile dysfunction, cognitive dysfunction, fatigue, depression, osteoporosis, changes in body composition, gynecomastia, anemia, and a form of

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metabolic syndrome characterized by abdominal obesity and insulin resistance[2]. The increased recognition of those side effects enhanced the appeal of reducing patient exposure to ADT.

2. BACKGROUND AND RATIONALE

In 1986, my colleagues and I first described intermittent androgen deprivation (IAD) for advanced prostate cancer in a report of 20 patients with metastatic disease treated with diethylstilbestrol, in whom the therapy was discontinued once they demonstrated a good clinical response. Diethylstilbestrol was resumed when the bone metastases became symptomatic again. The goals were to reduce the side effects of therapy and to improve quality of life (QOL)[3]. At the time, prostate-specific antigen (PSA) was not available as a biomarker of response or recurrence. That experience showed that treatment could be discontinued and patients would continue to demonstrate a clinical response upon re-treatment.

Around the same time, Nicholas Bruchovsky, an endocrinologist at the University of British Columbia with an interest in ADT, proposed what was then considered a radical hypothesis: that re-exposure of prostate cancer stem cells to androgen could re-induce differentiation and increase the apoptotic potential of previously androgen-sensitive cells that had acquired resistance. Using a Shionogi mouse model, he demonstrated a significant improvement in time to castration resistance with intermittent therapy[4–6]. The model was criticized because the cancer had been transplanted through 5 animals before it acquired castration resistance. Nonetheless, the data seemed to support Bruchovsky's concept.

Aside from the burden of side effects and the impact on QOL, cost reduction is a significant appeal of intermittent therapy. Although LHRH agonists are modest in cost (approximately $300–$400 monthly) compared with many cancer drugs, their widespread use means that they represent a large component of the outpatient cancer budget in Canada. A reduction in drug requirements of 50%–75% is attractive.

Thus, IAD is appealing on many fronts: improved QOL, reduced side effects, important cost reductions, and perhaps improved cancer survival. Few therapeutic innovations can make all of those claims.

3. PHASE II STUDIES

Between 1990 and 2004, many prospective trials of IAD were reported. Most were phase II or retrospective, and also single-institution series with relatively small numbers of patients. In the off-treatment interval, QOL was consistently improved, although most of the studies failed to use validated QOL instruments. Most trials included patients with a mix of disease stages, from biochemical recurrence, to local recurrence, to metastatic disease. An overview of the phase II studies estimated the 5-year overall survival to be 86% in men with biochemical recurrence, 68% in men with metastatic disease, and 90% in men with localized disease[7]. Development of early castration-resistant disease was a relatively rare event[8].

The studies identified a number of prognostic factors for time to androgen-independent progression. Those factors included duration of the off-treatment interval, baseline PSA, and PSA nadir. In a large prospective Canadian trial, the time off treatment averaged 53% of the total cycle time, but in absolute terms, it declined with each succeeding cycle, ranging from 63.7 weeks in cycle 1 to 25.6 weeks in cycle 5[9–11]. Of course, none of the trials was able to address the key question of the impact of IAD on survival.

4. PHASE III TRIALS

The results of several pivotal phase III trials have been reported or published recently (see Table I). The studies reporting survival data[13,17,18,21] showed no difference in overall and prostate cancer–specific survival between groups. However, those studies were underpowered and contained patients with both metastatic and nonmetastatic disease.

Two large trials with long-term follow up and homogeneous patient populations—the PR.7[19] and Southwest Oncology Group (SWOG) 9346 trials[20], intended as companion studies—were designed to address the impact of ADT on cause-specific and overall survival in a definitive fashion. Both were designed as noninferiority studies. The results, which are somewhat contradictory, are fascinating.

The PR.7 trial, in nonmetastatic patients, was led by the NCIC and supported by SWOG and the U.K. Coordinating Committee on Cancer Research. It enrolled 1386 patients with a PSA level greater than 3 ng/mL more than 1 year after primary or salvage radiotherapy for localized prostate cancer. Treatment with IAD was provided in 8-month cycles, with nontreatment periods determined according to PSA level. The primary endpoint was overall survival. Secondary endpoints included quality of life, time to castration-resistant disease, and duration of nontreatment intervals. Median follow-up was 6.9 years. In the intermittent therapy group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial entry threshold occurred in 79%. Patients on the intermittent arm were on treatment only 27% of the time. Benefits for QOL with IAD were seen in the domains of physical function, fatigue, urinary problems, hot flashes, libido, and erectile function. Deaths numbered 268 in the intermittent therapy group and 256 in the continuous therapy group. Median overall survival was 8.8 years in the intermittent therapy group compared with 9.1 years in the continuous therapy group [hazard ratio (HR): 1.02; 95% confidence interval (CI): 0.86 to 1.21]. The

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TABLE I Summary of phase III clinical trials of intermittent compared with continuous androgen deprivation therapy (ADT) in advanced prostate cancer

Reference (study name)	*Pts (n)*	*Setting*	*PSA triggers for ADT (ng/mL)*		*Induction*	*Treatment*	*Results*
			Stopped	*Started*			
de Leval *et al.,* 2002[12]	478	Advanced [T3–4, N+, M1 (40%), relapsed after RP]	<4	>10	7 Months goserelin acetate plus flutamide	Goserelin acetate plus flutamide	No difference in median PFS, lower CRPC in intermittent ADT arm
Miller *et al.,* 2007[13]	335	N+, M1	<4 or >90% reduction from baseline		6 Months goserelin acetate plus bicalutamide	Goserelin acetate plus bicalutamide	Similar OS, nonsignificantly improved PFS, improved QOL
	626	T3–4, M0/1	<1.0	>20 or	3 Months	Triptorelin	Similar PFS and OS,
Tunn *et al.,* 2007[14] (EC.507)	167	Rising PSA > 1 ng/mL after RP	<0.5 and no clinical progression	>3 or progression	3 Months leuprolide acetate flare prophylaxis with CPA	Leuprolide acetate flare prophylaxis with CPA	Similar PFS, improved QOL and fewer hot flushes in intermittent ADT arm
Salonen *et al.,* 2008[15]	564	Locally advanced, advanced, or M1	Minimum of 6 months; <10 or 50% of baseline	>20 or above baseline	6 Months goserelin acetate, flare prophylaxis with CPA	6 Months goserelin acetate, flare prophylaxis with CPA	Not reported
Verhagen *et al.,* 2008[16]	366	M1			CPA 100 mg 3 times daily for 3–6 months	CPA 100 mg 3 times daily for 3–6 months	QOL data (only) suggest better physical and emotional function and decreased cognitive function in intermittent ADT arm
Calais da Silva *et al.,* 2009[17] (SEUG)		Patients randomized who had PSA<4 or 80% decrease after induction ADT, 14% M1 disease		Symptomatic with PSA>10; also restarted for >20% of nadir in group that started because of decrease>80%	Triptorelin plus CPA	Pamoate plus CPA	Improved QOL
Mottet *et al.,* 2009[18]	173	M1 (to bone)	<4	>10 or symptomatic clinical progression	Leuprolin plus flutamide	Leuprolin plus flutamide	Similar OS and PFS, similar QOL
Crook *et al.,* 2012[19] (PR.7)	1365	PSA relapse post RT	Normalized	>10	8 Months LHRH agonist plus NSAA	Various LHRH agonists plus NSAA	Non-inferior OS and CSS, improved QOL
Hussain *et al.,* 2012[20] (SWOG 9346/PR.8)	1345	M1, PSA>5	<4.0	>20 or clinical progression	7 Months LHRH agonist plus NSAA	Goserelin plus bicalutamide	Inconclusive OS difference (HR: 1.09; NS), intermittent ADT worse in minimal metastatic disease

Pts = patients; PSA = prostate-specific antigen; SWOG = Southwest Oncology Group; LHRH = luteinizing hormone releasing hormone; NSAA = nonsteroidal antiandrogen; OS = overall survival; HR = hazard ratio; NS = nonsignificant; RT = radiation therapy; CSS = cause-specific survival; QOL = quality of life; PFS = progression-free survival; CPA = cyproterone acetate; CRPC = castration-resistant prostate cancer; RP = radical prostatectomy.

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associated 7-year cumulative rates of prostate cancer mortality were 18% and 15% respectively ($p = 0.24$).

The PR.7 trial is the first to definitively demonstrate equivalence in terms of overall survival and prostate cancer–specific survival in men randomized to IAD compared with continuous androgen deprivation (CAD). Time to castration resistance was longer in the IAD arm, likely reflecting a bias in the trial design. As originally constructed, patients off treatment with a rising PSA had to be placed back on therapy, with PSA being seen to rise again before they were deemed to have castration resistance. In fact, many patients had prolonged androgen suppression during the off-treatment interval, and their rising PSA reflected true castration resistance. That result was not foreseen at the time the trial was initiated in the mid-1990s. Thus, the time to androgen independence was biased in favour of the intermittent arm. The fact that prostate cancer deaths trended higher in the intermittent than in the continuous arm (balanced precisely by an increased number of non–prostate cancer deaths in the continuous arm) reinforces the suggestion that the difference in time to castration resistance was probably an artefact. Time to castration resistance was nonsignificantly different between the groups in several other phase III trials[14,17].

The SWOG 9346 trial was designed along similar lines to evaluate overall and disease-specific survival for IAD compared with CAD given to patients with metastatic prostate cancer. The study registered 1535 men with lymph node, visceral, or bone metastases and a PSA exceeding 5 ng/mL and placed them on 7 months of goserelin and bicalutamide. If PSA was less than 4 ng/mL by month 6, the men were then randomized to either discontinuation of therapy (IAD) or CAD. Treatment was reinitiated when PSA reached a baseline of 20 ng/mL and discontinued again after 7 months if PSA was less than 4 ng/mL. The trial was sized to demonstrate noninferiority with a delta of 1.2.

Approximately 90% of the patients have now died. Overall survival showed a nonsignificant trend to improvement in the CAD arm (HR: 1.09; 95% CI: 0.95 to 1.24). Median survival was 5.8 years compared with 5.1 years—a 7-month difference. A sub-analysis (not specified *a priori*) stratified by minimal disease (confined to axial skeleton and pelvis or to lymph nodes) and extensive disease (any or a combination of ribs, long bones, skull, or viscera) showed a benefit in the minimal-disease group (HR: 1.23; 95% CI: 1.02 to 1.49; $p = 0.034$) and no benefit in the extensive-disease group (HR: 0.95; 95% CI: 0.80 to 1.16). In the minimal-disease group, median overall survival was 5.2 years with IAD and 7.1 years with CAD. The authors claim that the study demonstrates the inferiority of intermittent therapy in that setting.

The interpretation of SWOG 9346, which was still unpublished at the time this manuscript was written, is controversial. It reflects a somewhat arcane statistical controversy over the correct interpretation of noninferiority trials. The issue is the significance of a result in which the confidence limits cross both unity and the pre-specified delta—that is, the minimum difference thought to be clinically significant at the time of trial design (for interested readers, I recommend an informative article by Piaggio *et al.*[22] on the interpretation of noninferiority trials). First, the primary endpoint showed no significant difference between the two arms (95% CI: 0.95 to 1.24). The fact that the CI crossed the pre-specified delta does not imply inferiority; rather, it means that the results are inconclusive with respect to noninferiority, which cannot be ruled out. Coincidentally, superiority also cannot be ruled out. Importantly, those findings also apply to the results in the minimal metastatic disease group. Because both sides of the 95% confidence limits were not beyond the delta of 1.2, even that result is inconclusive for noninferiority. Second, the stratification analysis was conducted *post hoc,* making it hypothesis-generating, not proof. Third, considering these two large well-conducted studies together, PR.7 shows noninferiority for IAD in nonmetastatic disease, and SWOG 9346 purports to show both inferiority of IAD in minimal metastatic disease and noninferiority in extensive metastatic disease. It is a struggle to make biologic sense of the supposed inferiority of IAD in minimal metastatic disease, encased between the bookends of the apparent noninferiority of IAD in both nonmetastatic and extensive metastatic disease. A possible explanation is that at the favourable (nonmetastatic) and unfavourable (extensive metastatic) ends of the spectrum, ADT adds little or nothing to patient survival, and therefore whether treatment is intermittent or continuous is irrelevant, and that, for the minimal metastatic disease where ADT does make a difference, continuous is seen to be better than intermittent. In the context of the interpretation of the earlier-mentioned SWOG data, the foregoing interpretation is only a hypothesis.

The intermittent arm of PR.7 experienced 9% more prostate cancer deaths, but that difference did not achieve significance. It is, of course, possible that the trial was simply underpowered to show a small difference in cancer-specific survival. Given that the increased mortality from non–prostate cancer death in the continuous arm perfectly balanced that increase in cancer deaths, the question seems moot. One might argue that, if a population of men without cardiovascular morbidity were to be treated, a difference in overall survival might emerge. Again, that suggestion is a hypothesis.

The bottom line is that the substantial QOL benefits of intermittent therapy, combined with the apparent protective effects on bone mineral density (BMD), surpass the hypothetical survival benefits of continuous therapy, which failed to emerge in two studies following almost 3000 patients. Further, in clinical practice, patients who are not likely to benefit from intermittent therapy can be identified early (by clinical parameters

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or by observation during a short off-treatment interval) and switched to continuous therapy.

5. TESTOSTERONE DURING IAD

The improved QOL during intermittent therapy is a function of testosterone recovery in the off-treatment cycle. The rate of recovery after discontinuation of ADT is quite variable. It is a function of duration of ADT treatment, patient age, baseline testosterone, and ethnicity[23]. Further, the rate of recovery tends to lag with successive cycles of treatment. The Canadian phase II study demonstrated that most of the recovery of testosterone occurs by 5 months in cycle 1[9]. Recovery of serum testosterone to 7.5 nmol/L or more was observed in 75%, 50%, 40%, and 30% of men in cycles 1,2, 3, and 4 respectively.

The off-treatment duration reported in prospective phase III trials ranged from 50% to 82%[12,13,17,19]. It was 73% in the PR.7 trial, a level higher than that reported in phase II trials, in which patients spent a mean of 39% of their time off treatment[7]. Most studies have shown that the off-treatment duration diminishes with successive cycles (in spite of the slower recovery of testosterone). That finding presumably reflects the acquisition of a castration resistant phenotype, with more rapid recovery of PSA.

The equivalent outcomes found with IAD present a conundrum when compared with other recent data[24,25] suggesting that patient outcomes are superior on CAD if testosterone levels are maintained below 20 ng/mL. Testosterone rises during the off-treatment interval, and yet that rise has no apparent adverse effect on survival. This apparent contradiction may be explained by the heterogeneous sensitivity of prostate cancer cells to androgen exposure. Much experimental data has demonstrated the variable response of prostate cancer cells to androgens[26]. Androgens at high concentrations induce cell cycle arrest. In one model, a concentration of 0.1 nmol/L of R1881 induced maximal proliferation in one subtype of LNCaP and maximal proliferation inhibition in another subtype. It is plausible that, on the one hand, IAD may be equivalent to CAD in terms of survival (by re-inducing apoptotic potential during the on-treatment interval) and that low levels of testosterone may be important during the on-treatment interval by inducing apoptosis in cells that are resistant to "partial" androgen ablation and that would otherwise survive (see Figure 1).

6. QUALITY OF LIFE

In most studies, QOL is improved during the off-treatment interval[13,17,19,21,27]. Some studies failed to show a QOL benefit[17,18]. In the study by the South European Uroncological Group (SEUG), QOL was similar between arms, although lower rates of hot flashes, gynecomastia, and headaches were seen in the intermittent arm[17].

Bone mineral density declines with ADT, increasing the risk of osteoporosis and fracture. Only limited data are available on the benefit of intermittent therapy in BMD preservation. One study[28] of BMD in 72 patients undergoing IAD for a period of 3 years showed that BMD decline was attenuated during the off-treatment interval compared with the initial 9 months. Moreover, BMD change in the off-cycle was strongly associated with the level of testosterone recovery, with greater BMD losses in men whose testosterone did not recover to levels above 5 nmol/L. Another study reported an odds ratio of 2.14 for osteoporosis ($p = 0.032$) in men on CAD compared with IAD[29].

Androgen deprivation therapy induces anemia, with hemoglobin declining an average of 15%[9]. This anemia is not closely correlated with measured QOL changes[30], but hemoglobin levels are a function of testosterone. In a detailed analysis of 110 patients in a Canadian phase II trial of IAD[9], hemoglobin declined an average of 11 g/L during treatment and then recovered to baseline during the off-treatment phase. Another study[31] estimated that, in 50% of patients, hemoglobin levels recovered during the off-treatment cycle of IAD.

Metabolic syndrome and associated cardiovascular toxicity is a complication of ADT. Some data suggest that this toxicity is restricted to patients with pre-existing comorbidity[32]. The impact of IAD is unknown. The PR.7 trial reported 8% more non–prostate cancer deaths in the continuous arm, but that difference was not a result of an increase in any one particular cause of death. The SEUG phase III trial[17] had fewer cardiovascular deaths in the intermittent arm (52 vs. 41). Similarly, the degree to which metabolic syndrome is attenuated by IAD has not been quantified. Malone *et al.*[31] showed that weight remained stable in men on IAD, and that men on continuous therapy experienced a 3%–5% weight gain. That finding suggests that weight gain during ADT therapy is offset by weight loss during the off-treatment cycle.

Since the first publication on IAD[3], an improvement in sexual function during the off-treatment cycle of intermittent therapy has been seen. Of 10 patients rendered impotent in that series, 9 regained potency during the initial off-treatment phase. More recent data suggest that sexual potency recovers in approximately 50% of patients during the off-treatment cycle[13,31]. Results from the SEUG study showed increased sexual activity at 15 months after randomization in the IAD arm compared with the CAD arm (28% vs. 10%)[19]. The PR.7 trial also showed an improvement in sexual activity during the off-treatment interval.

7. WHO SHOULD RECEIVE IAD?

The commonest indication for IAD in the Western world, where PSA screening and early detection of

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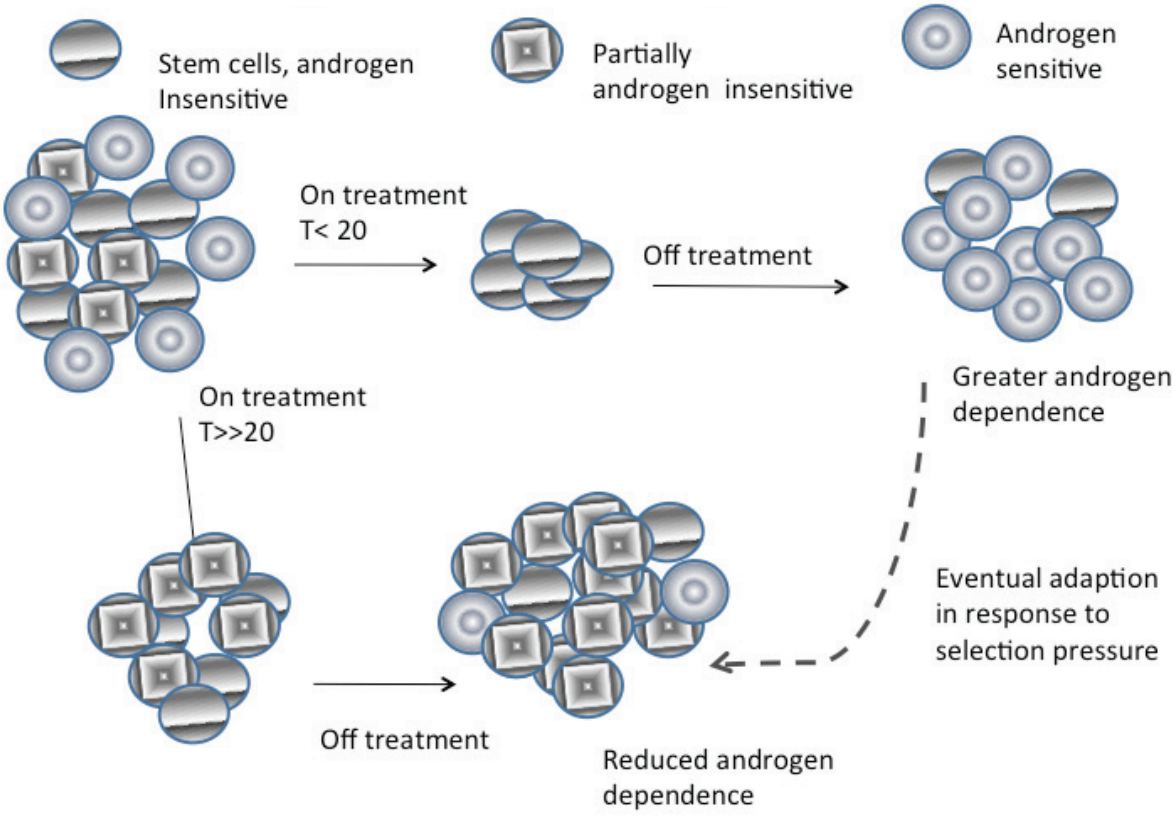

FIGURE 1 A three-cell-type model is consistent with the apparent conundrum of improved survival with low nadir testosterone on androgen deprivation therapy (ADT) and noninferiority of intermittent ADT, in which testosterone (T) returns to normal levels during the off-treatment interval. More effective ADT, achieving serum T < 20 ng/mL, would result in cell death in both the androgen-sensitive and partially androgen-sensitive subpopulations. On repopulation, the result is a highly androgen-sensitive population of cells and a more prolonged time to castration resistance. Failure to adequately ablate T below 20 ng/mL could result in the persistence of a partially androgen-insensitive subpopulation, which repopulate upon re-treatment, accelerating progression to androgen-independence.

prostate cancer are widespread, is biochemical recurrence after definitive therapy. Most such patients have no evidence of bone metastases. Based on the data reviewed here so far, IAD should be used in most of them. Based on the (as yet unpublished, but presented—and widely available online) SWOG study in metastatic disease, caution is warranted in men with bone metastases. As mentioned already, the interpretation of the SWOG study is controversial. Regardless, the benefit of IAD in men with bone metastases is less because of decreased life expectancy and shortened off-treatment intervals. However, some of these patients demonstrate a robust and sustained response to ADT. The nadir PSA on treatment has been demonstrated to be a predictor for duration of response.

Thus, a practical approach is to initiate ADT therapy and to re-evaluate the patient based on PSA and clinical response. In patients who have a complete biochemical response (with undetectable levels of PSA), a trial of IAD should be considered. Should the off-treatment interval prove to be short because of rapid PSA recovery, these patients would be restarted relatively soon on continuous therapy. However, some patients will enjoy a prolonged off-treatment interval notwithstanding the presence of bone metastases, and they stand to benefit from such an approach. The failure to achieve a low nadir PSA should preclude intermittent therapy. Similarly, patients with bulky tumours, a significant burden of nodal and bone metastases, PSA above 100 ng/mL, rapidly rising PSA (more than 5 ng/mL per month), and severe pain are poor candidates for IAD[15,33].

Some constituencies have used IAD for treatment of localized prostate cancer[34]. I do not support that approach. Patients with asymptomatic early prostate cancer are best treated with active surveillance or local therapy. In elderly patients, "watchful waiting" (in the absence of the opportunity for definitive management) is appropriate. The systemic toxicity of ADT, particularly in men with pre-existing cardiovascular morbidity, precludes its rational use in that setting. The SAKK (Swiss Group for Clinical Cancer Research) 09/88 and European Organisation for Research and Treatment of Cancer 30891 trials[35,36] showed that,

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in patients not suitable for local curative treatment, the benefit of ADT was modest. The benefits of IAD do not warrant the use of this approach in patients not requiring treatment.

Patients with node-positive disease after radical prostatectomy have a survival benefit from adjuvant ADT[37]. The trial by Messing and colleagues compared lifelong ADT with delayed ADT in these patients, showing a significant survival benefit[38]. It is likely, however, that many patients do not require such prolonged treatment, particularly those with either a slow natural history or a high competing death risk. In those patients, IAD may avoid overtreatment by enabling the selection of patients with more indolent tumours. In the phase III German study of IAD compared with CAD (which showed no difference in overall survival), the subset of patients with node-positive disease showed a strong trend to improved time to progression with IAD ($p = 0.07$)[13]. Our current practice is to discontinue adjuvant ADT in node-positive patients after 2–3 years after radical prostatectomy, and then to use IAD as necessary.

8. DURATION OF INDUCTION AND PSA TRIGGERS

An unresolved question in the field is the appropriate PSA trigger for initiating ADT in men with biochemical failure. The only data from randomized trials pertaining to this question are those from the European Organisation for Research and Treatment of Cancer 30891 trial, which showed an 11% survival benefit in men treated with primary ADT for localized prostate cancer. In that study, the benefit of early treatment was seen at a PSA threshold of 20 ng/mL for men under 70 years of age and of 50 ng/mL for men older than 70. Those values represent approximate PSA thresholds for initiating treatment in men with biochemical failure.

Thus, the first component of IAD in the nonmetastatic patient with PSA failure is to delay therapy initiation until PSA reaches a level of 20–50 ng/mL, depending on age (acknowledging that this approach is more conservative than conventional practice).

After initiation of ADT, the mean PSA reduction to nadir is 95.2% regardless of stratification group[11]. In most patients, 8–9 months are required to achieve a PSA nadir. After 2 years or more of continuous treatment, 50% of patients will fail to recover testosterone. Thus, an induction period of 2 years is excessive for IAD. An 8- to 9-month period of ADT induction seems reasonable. (However, the SEUG study used only 3 months of induction and showed noninferior survival.) Studies comparing various durations of induction ADT are currently ongoing (see Table I).

Most of the phase III trials required that a PSA of less than 4 ng/mL be achieved before ADT discontinuation. The PSA triggers for re-treatment vary between studies, but are generally set between 10 ng/mL and 20 ng/mL. Shaw *et al.*[7], in a meta-analysis of phase II trials, demonstrated improved survival for patients whose PSA threshold to restart was less than 15 ng/mL.

Close scrutiny for clinical progression is mandatory. An unexpected phenomenon in the PR.7 trial was the relatively large number of patients who experienced prolonged androgen suppression in the off-treatment interval and who developed castration-resistant disease despite being off treatment. Thus, patients must be monitored closely for PSA and testosterone at least every 3 months while off treatment.

Most phase III trials with published results used the combination of a LHRH agonist and an antiandrogen for flare blockade. The role of combined androgen blockade in intermittent therapy is unproven. Blockade of flare is clearly rational, given the short duration of treatment. Some modelling of prostate cancer kinetics suggests that more aggressive hormonal blockade during the treatment interval is of benefit, but those benefits have yet to be demonstrated in clinical practice (Figure 1). The use of LHRH antagonists in IAD, which may be associated with more prompt recovery of testosterone, is the subject of current clinical trials.

9. PROGNOSTIC FACTORS

After treatment with ADT, PSA nadir is a strong predictor of early progression[13,17,27]. In patients on continuous therapy, those whose PSA remained detectable had a 15 times greater likelihood than those with an undetectable PSA of progressing to castration-resistant prostate cancer within 24 months of starting ADT[39]. In men on IAD, the nadir value is also predictive[11,17]. After the first cycle, a PSA nadir below 0.1 ng/mL is favourable, and failure to nadir below 0.4 ng/mL is associated with a doubled to tripled risk of developing castration-resistant prostate cancer and clinical progression[40].

Not surprisingly, the duration of the off-treatment cycle predicts for time to progression. Two studies[40,41] showed that a shorter off-treatment cycle confers a 2.9 risk for progression to castration-resistant prostate cancer and a 3.8 risk for death. This ability to infer prognosis during intermittent therapy allows for identification of patients at higher risk of progression and becomes relevant as new therapies for advanced prostate cancer become available.

10. FUTURE DIRECTIONS

Several treatments have been studied during the off-treatment cycle of IAD, including COX-2 inhibitors[42], thalidomide[43], pazopanib[44], and finasteride[45]. One retrospective study demonstrated increased off-treatment time (31 months vs. 15 months) in patients who used finasteride during the off-treatment interval. A randomized multicentric trial (AVIAS) is currently investigating the benefit of 5-α-reductase inhibitors in IAD.

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11. SUMMARY

Intermittent androgen deprivation is an appropriate option for many patients needing ADT for advanced or recurrent prostate cancer. The results of phase III studies now establish that, in men with biochemical failure, IAD offers noninferior survival, with fewer side effects of therapy and better QOL. It also has a role in selected patients with metastatic disease. The benefits it offers to patients (improved QOL and reduced comorbidity) and to society (reduced costs) warrant its widespread utilization.

12. CONFLICT OF INTEREST DISCLOSURES

LK has participated on advisory boards for AstraZeneca, Ferring Pharmaceuticals, Abbott Laboratories, and Sanofi-Aventis. He has received research funding from AstraZeneca, Ferring Pharmaceuticals, and Abbott Laboratories.

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