Intermittent Versus Continuous Androgen Deprivation Therapy

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Abstract

Androgen deprivation therapy (ADT) has been the standard of care for metastatic prostate cancer for decades; however, the choice of continuous or intermittent administration is a matter of debate. Two large phase III trials have reported results comparing these 2 forms of ADT administration. The National Cancer Institute of Canada (NCIC) PR-7 trial studied men with an increasing prostate-specific antigen (PSA) level and no evidence of metastatic disease after definitive or salvage radiation therapy and radical prostatectomy. The Southwest Oncology Group 9346 trial studied men with newly diagnosed hormone-sensitive metastatic disease. The primary end point in both trials was overall survival with a noninferiority design. The NCIC trial showed that the overall survival in men treated with intermittent ADT was not inferior to that of men treated with continuous ADT, but the SWOG trial was inconclusive regarding noninferiority. Certain domains of quality of life were better in the intermittent arms of both trials. If using ADT in the setting of biochemical relapse, intermittent ADT should be strongly considered over continuous ADT, except perhaps in patients with Gleason score of 8 or higher. In men with metastatic disease, continuous ADT remains the standard of care, because the SWOG trial did not establish noninferiority of intermittent ADT with respect to survival. However, for those with significant side effects from ADT, establishing the risk group, as determined by PSA value after 7 months of ADT or the presence of pain at diagnosis, may help guide the choice of intermittent versus continuous ADT in men with metastatic disease. (*J Natl Compr Canc Netw* 2014;12:727–733)

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Androgen deprivation therapy (ADT) has been the standard of care for metastatic prostate cancer since 1941, when Huggins and Hodges[1] demonstrated the effect of androgens on prostate cancer and the impact of orchiectomy on bone pain symptoms. Hot flashes, loss of libido, and loss of potency were well-known side effects of orchiectomy. Starting in the 1980s, testosterone could be lowered to castrate levels with injections of gonadotropin-releasing hormone (GnRH) analogs, although these agents conferred the same toxicity as orchiectomy. After the test for prostate-specific antigen (PSA) was approved by the FDA in 1986, a new population of men was identified who had no evidence of metastatic disease other than an increasing PSA level after primary therapy for prostate cancer, often called *biochemical relapse*. These men had no symptoms of cancer, yet were often treated with ADT because of concern for cancer progression. The side effects and toxicities of ADT became more apparent and assumed greater importance in these otherwise asymptomatic men.

Side Effects of ADT

Despite the positive effects that ADT has on cancer and its related morbidities, patients report a myriad of well-recognized side effects resulting from castrate levels of testosterone (Table 1).[2] ADT has the potential to cause many physical and emotional changes that can diminish longevity (eg, metabolic abnormalities, obesity, sarcopenia, exacerbation of cardiovascular morbidity and mortality, weakened bones resulting in fracture) and seriously impact the quality of life of both the patient and, indirectly, his partner (eg, fatigue, hot flashes, decreased libido, loss of masculine physical characteristics, depression). These side effects have been significant enough to explore dosage and cycling options for ADT to delay disease progression and attenuate side effect burden.

Table 1 Potential Complications From Androgen Deprivation Therapy From the Patient Perspective

What Physicians Tell Patients	What Patients Feel	What Patients See	What Patients Do Not See
Loss of libido	Fatigue or loss of energy, initiative	Weight gain	Loss of bone mineral density
Erectile dysfunction	Aches and pains	Loss of muscle mass and strength	Changes in lipids
Hot flashes	Low spirits, depression	Increased subcutaneous tissue, especially in hips, thighs, and abdomen	Glucose intolerance, diabetes
	Emotional lability	Gynecomastia	Anemia
	Cognitive changes	Decrease in testicular size and penile length	Increased cardiovascular risk in those with history of MI or CHF
		Loss of body hair	

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction.

Modified from Higano C. Androgen deprivation therapy: monitoring and managing the complications. Hematol Oncol Clin North Am 2006;20:909–923, and Chi KN, Nguyen PL, Higano CS. Androgen deprivation for prostate cancer. Available at: http://meetinglibrary.asco.org/content/24-132. Accessed April 2, 2014; with permission.

History of Intermittent Therapy

Whitmore[3] was the first to report on the use of intermittent endocrine therapy. As described in their retrospective review,[3] their 17 men with symptomatic metastatic disease were treated with estrogen until their pain subsided. Thereafter, estrogen was stopped until symptoms recurred, and then it was resumed. Of the 10 patients who were potent before but not after starting estrogen therapy, 9 resumed sexual activity with 3 months of stopping estrogen.

Concurrently, Akakura et al[4,5] studied the concept of intermittent androgen suppression, first using the androgen-dependent Shionogi mouse mammary carcinoma line and later implanting LNCaP cells into male mice. After castration and tumor regression, the remaining tumor was transplanted into intact male mice successively in this manner until androgen-independent growth occurred. Compared with castration alone, androgen dependence was maintained longer with intermittent reexposure of the cell lines to androgen. This led to the hypothesis that intermittent ADT would delay time to androgen-independent progression. Hence, intermittent ADT became an interesting approach from the standpoint of both delaying time to androgen-independent growth and improving patients' quality of life (as described by Klotz et al[3]). Numerous small phase II studies demonstrated the feasibility of this approach in both metastatic and nonmetastatic disease,[6,7] leading to larger phase II and some small phase III trials. These trials often had different treatment schedules in terms of duration and type of ADT, time off-therapy, and entry criteria.[8–10]

Phase III Trials of Intermittent Versus Continuous ADT

In light of this interest in delaying time to androgen independence and benefitting patient quality of life, 2 large phase III trials were designed to compare intermittent and continuous ADT. The SWOG 9346 trial studied men with newly diagnosed, hormone-sensitive, metastatic disease,[11] and the National Cancer Institute of Canada (NCIC) PR-7 trial treated men without evidence of metastases who had an increasing PSA level after either primary or salvage radiation and radical prostatectomy.[12]

Both of these phase III trials were designed to show that intermittent ADT was not materially worse than continuous ADT in a so-called noninferiority design. In a noninferiority trial, the difference in response between the active control (continuous ADT) and the experimental arm (intermittent ADT) must be less than a prespecified noninferiority margin. If the difference is less than this margin, then the experimental arm (intermittent ADT) can be considered not materially worse or noninferior to continuous ADT. If, however, the difference is greater than the noninferiority margin, then a conclusion about the differences in the treatments cannot be made and the results of the trial are considered inconclusive.

Both the SWOG and NCIC trials also used the same intermittent therapy regimen, consisting of 8 months of ADT followed by a variable time off ADT as determined by a threshold value of serum PSA (Figure 1). In either trial, if the PSA at the end of

8 months was greater than 4 ng/mL, patients were treated with continuous ADT. During the off-treatment interval, if the PSA increased to the threshold value after only 2 to 3 months, then continuous ADT was administered, because any advantage of intermittent therapy would be lost. Tables 2 and 3 summarize the characteristics and overall survival results of each trial.

SWOG 9346

The results of the SWOG trial were inconclusive in terms of showing that the overall survival (OS) of patients on the intermittent arm was not inferior to that of those treated with continuous ADT.[11] A subset analysis by extent of disease, however, suggested that patients with minimal disease (defined as metastases to the spine, pelvis, and/or lymph nodes) had inferior median survival on intermittent ADT compared with continuous ADT (5.4 vs 6.9 years, respectively), whereas those with extensive disease (defined as metastases to ribs, long bones, or viscera) had similar median OS whether on intermittent or continuous ADT (4.9 vs 4.4 years, respectively). These results are certainly not intuitive, and could be related to the PSA threshold for retreatment in the intermittent ADT arm and/or the definitions of minimal and extensive disease.

An alternative understanding of the data that makes more sense comes from the subgroup of men who had pain at study entry compared with those with no pain. The asymptomatic men had similar median OS whether treated with intermittent (5.7 years; 95% CI, 5.1, 6.7) or continuous ADT (6 years; 95% CI, 5.5, 6.8), whereas those with pain had better OS with continuous ADT.

Quality of life for 5 prespecified outcomes (erectile dysfunction, libido, vitality, mental health, and physical functioning) was measured at months 3, 9, and 15 after randomization. Quality of life at month 3 after randomization (3 months off ADT in the intermittent ADT arm) was a coprimary end point. At this time point, measures of potency and mental health were significantly better and libido trended toward improvement in the intermittent ADT arm. At 9 months, 4 of the 5 outcomes were better in the intermittent ADT arm, but were not statistically significant. By 15 months, 78% of men on the intermittent ADT arm were back on ADT, and only physical functioning was better in the intermittent ADT arm, but again, this was not statistically significant.

NCIC PR-7

The NCIC trial established that intermittent ADT was not inferior to continuous ADT in men with nonmetastatic disease.[12] More prostate cancer deaths occurred in the intermittent ADT arm, but these were balanced by 7% more non–prostate cancer deaths in the continuous ADT arm. An unplanned

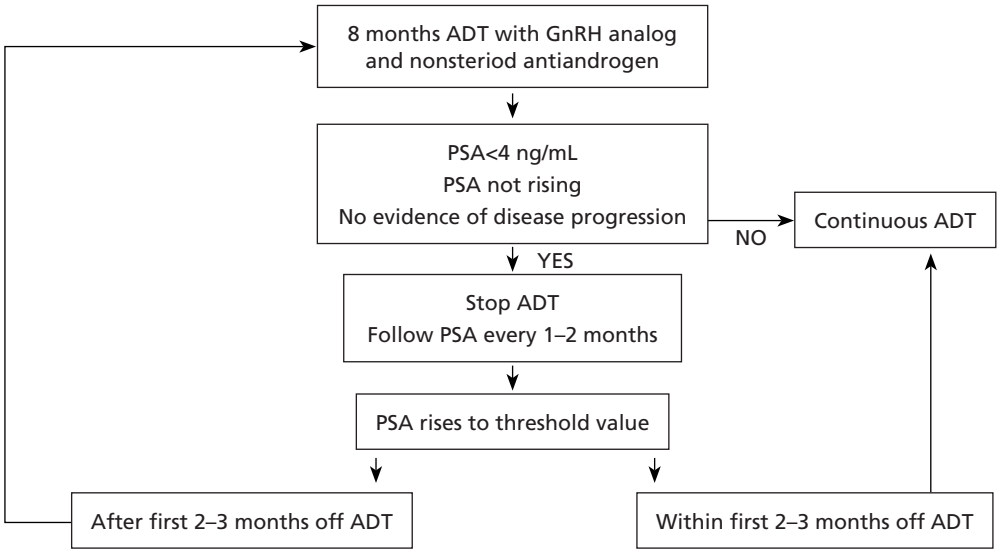

Figure 1 Intermittent ADT regimen for SWOG 9346 and NCIC PR-7 trials. SWOG threshold value: PSA> 20 ng/mL or baseline if PSA < 20 ng/mL at start (this may be too high, consider lower threshold); NCIC threshold value: PSA > 10 ng/mL.
Abbreviations: ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen.

Table 2 Trial Characteristics of NCIC PR-7 and SWOG 9346

	NCIC (Nonmetastatic)	SWOG (Metastatic)
Number randomized	1386	1535
Accrual period	1999–2005	1995–2008
Randomization	At study entry	If PSA <4 ng/mL after 6 and 7 mo of ADT
Primary end points	OS	OS QoL at 3 mo after randomization
Statistical design	Noninferiority	Noninferiority
PSA at baseline	>3 ng/mL	≥5 ng/mL
ADT	GnRH analog and minimum 4 wk antiandrogen	Goserelin and bicalutamide
Continuous ADT	Orchiectomy allowed	No patients had orchiectomy
Intermittent ADT	8 mo of ADT	8 mo of ADT
PSA threshold to resume ADT	≤10 ng/mL	PSA 20 ng/mL or PSA at baseline if PSA <20 ng/mL at entry
Median follow-up	6.9 y	9.8 y

Abbreviations: ADT, androgen deprivation therapy; GnRH, gonadotropin-releasing hormone; NCIC, National Cancer Institute of Canada; OS, overall survival; PSA, prostate-specific antigen; QoL, quality of life; SWOG, Southwest Oncology Group.

subset analysis by Gleason score showed that for patients with Gleason scores 8 through 10, although not statistically significant, a 14-month difference in median survival favored the continuous ADT arm.[9]

Hot flashes, libido, and urinary symptoms were improved significantly in the intermittent ADT arm, with fatigue trending toward improvement. Physical, role, and global health scores were slightly, but not significantly, better in the intermittent ADT arm.

Intermittent Versus Continuous Therapy: Decision-Making Considerations

The statistical plans for the NCIC and SWOG trials made assumptions about median survival that proved to be incorrect. In each case, the median OS was longer than expected based on historical data: 9 years versus 7 years for the nonmetastatic population and 5.8 years vs 2.9 years for patients with metastatic disease. Given the duration of time during which these trials were conducted and changes in standards of health care over that same period, this is not surprising.

Table 3 OS and Cause of Death for NCIC PR-7 and SWOG 9346

	NCIC (Nonmetastatic)		SWOG (Metastatic)	
	Intermittent ADT	Continuous ADT	Intermittent ADT	Continuous ADT
Median OS	8.8 y	9.1 y	5.1 y	5.7 y
HR	1.02 (90% CI, 0.86–1.21)		1.10 (95% CI, 0.99–1.23)	
Prostate cancer mortality	41%	34%	80%	73%
Non–prostate cancer–related mortality	28%	36%	20%	27%

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; NCIC, National Cancer Institute of Canada; OS, overall survival; SWOG, Southwest Oncology Group.

The strengths of these trials include their size, the duration of follow-up, use of comparable ADT regimens, use of quality-of-life questionnaires, and OS rather than time to progression as the primary end point. Despite the challenge of longer-than-anticipated survival times, both of these large phase III trials yielded valuable data that can be used to counsel and advise patients with respect to the decision to use intermittent versus continuous ADT (Table 4).

Nonmetastatic Relapse

One factor that was not addressed by the NCIC trial was the timing of initiation of ADT for men with biochemical relapse. A greater understanding now exists of the natural history of men biochemical relapse based on PSA kinetics and Gleason score.[13] A rapid PSA doubling time (PSADT) and/or Gleason score of 8 or higher are associated with poorer outcomes, and these patients should probably be offered immediate ADT or treatment on a clinical trial. Alternatively, those with a prolonged PSADT greater than 12 months and/or Gleason scores less than 8 are at lower risk for progression to metastatic disease and can probably be observed if the patient is willing.[13] Another issue not addressed by the NCIC trial was the timing of salvage radiation therapy. Men who have biochemical relapse after radical prostatectomy without prior radiation should be considered for salvage radiation under certain circumstances,[14] because this is a potentially curative approach for a highly select group of patients.

Given the subgroup Gleason analysis from the NCIC trial and the knowledge that patients with

Table 4 Factors to Consider When Choosing Intermittent Versus Continuous ADT by Disease State

Recommendation	Rationale
Biochemical Relapse	
Intermittent ADT is a reasonable option if ADT is to be administered	NCIC PR-7 data: intermittent ADT is noninferior to continuous ADT
Patients with Gleason score of 8 should consider continuous ADT over intermittent ADT	NCIC PR-7 unplanned analysis shows a nonsignificant 14-mo difference in median survival favoring continuous arm
Metastatic Disease	
After 7 mo of ADT, define risk category:	SWOG 9346 data showed that PSA at 7 mo was an independent predictor of survival (median):
• Low (PSA ≤0.2 ng/mL): base decision on symptoms	6.25 y
• Intermediate (PSA >0.2 but ≤4.0 ng/mL): same as low risk	3.70 y
• High (PSA >4.0 ng/mL): continuous ADT	1.10 y (likely to have early CRPC)
Symptoms of ADT after 7 months:	
• Few or none: consider continuous ADT because no QoL benefit will be gained	Intermittent ADT is more labor-intensive, especially in metastatic disease
• Significant: consider intermittent ADT for QoL reasons; counsel patient regarding the uncertainty of survival impact	QoL better in intermittent arm; benefit likely underestimated because of timing of assessments
Presence of pain at diagnosis, consider continuous ADT	Subgroup analysis of SWOG 9346 suggests that continuous ADT is more beneficial than intermittent ADT
If using intermittent ADT, consider lower PSA threshold to resume ADT	SWOG 9346 PSA threshold to resume ADT was 20 ng/mL; this is probably too high

Abbreviations: ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; NCIC, National Cancer Institute of Canada; PSA, prostate-specific antigen; QoL, quality of life; SWOG, Southwest Oncology Group.

nonmetastatic disease and a Gleason score of 8 or higher experience progression to metastatic disease more quickly, continuous ADT is probably a better choice. Those with a Gleason score less than 8 can be offered intermittent or continuous ADT, with the understanding that intermittent ADT may have benefits in terms of quality of life. Although not measured in the NCIC trial, other benefits of intermittent ADT have been documented, such as preserving bone mineral density.[15] Thus, intermittent ADT may be a better option in terms of metabolic, cardiovascular, and bone health, regardless of quality-of-life measures, especially for patients who chose ADT despite low-risk PSA kinetics and Gleason score.

Metastatic Disease

Counseling men with metastatic disease is more complicated. Continuous ADT is currently the standard of care, although many physicians and patients still prefer intermittent ADT. Data from an earlier report of the SWOG study can inform decision-making by providing a basis for risk stratification. An analysis of all patients enrolled on the study before randomization showed that the absolute PSA value (not necessarily the nadir) after the first 7 months of ADT was a strong independent predictor of survival[16] (Figure 2). Patients with a PSA level of 0.2 ng/mL or less had a median OS of 6.25 years, whereas those who did not achieve a PSA level of less than 4.0 ng/mL had a median survival of 1.10 year. Those with a PSA level greater than 0.2 ng/mL but 4.0 ng/mL or less had an intermediate median OS of 3.70 years. In addition to this stratification, the presence of pain at diagnosis and the side effects from ADT should be factored into the decision-making process (Table 4). For example, if a patient without symptoms at diagnosis, who could otherwise be offered either continuous or intermittent ADT, has a PSA greater than 4 ng/mL after 7 months of ADT, continuous ADT is probably a better choice. The same asymptomatic patient with a low-risk PSA value could be offered intermittent ADT, but this may be worthwhile only if he has significant adverse symptoms from ADT. For most men who experience few, if any, symptoms from ADT, there is no impetus based on quality-of-life benefit to choose intermittent ADT. Although continuous ADT resulted in more non–prostate cancer–related deaths in the nonmetastatic setting, most men with metastatic disease die of prostate cancer, not from competing comorbidities. Therefore, for these few

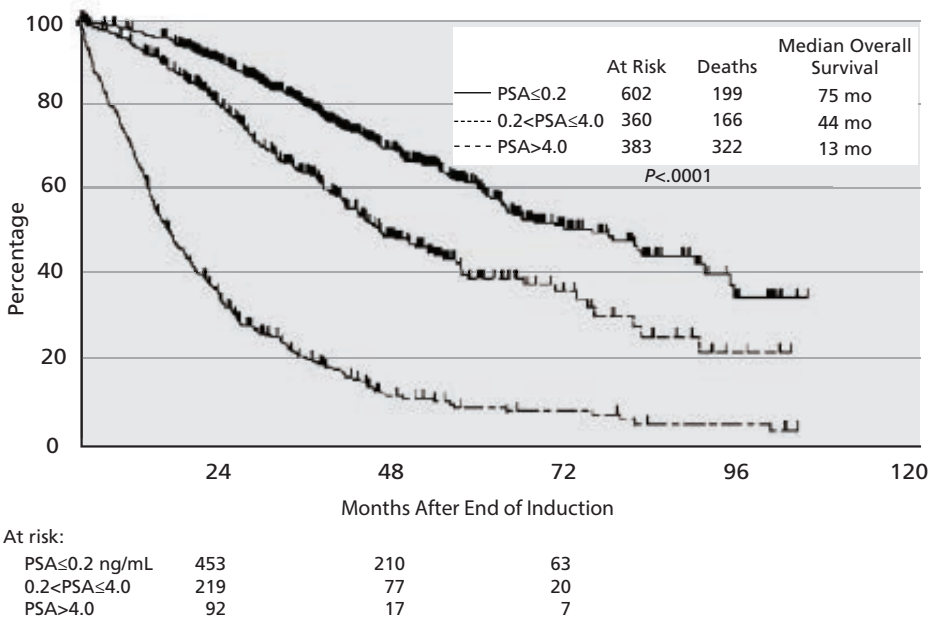

Figure 2 Overall survival by PSA after 7 months of ADT on SWOG 9346.
Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; SWOG, Southwest Oncology Group.
From Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–3990; with permission.

men with no ADT-related symptoms, irrespective of pain or risk group, continuous ADT makes the most sense, because it is less work-intensive for the physician and requires less monitoring of the patient.

Conclusions

Intermittent ADT confers benefit in some measures of quality of life, although the preclinical findings that it delays onset of castration resistance and death compared with continuous ADT were not confirmed in 2 large phase III clinical trials. In the nonmetastatic setting in the NCIC trial, intermittent ADT was not inferior to continuous ADT with respect to OS, and was associated with better hot flash, libido, and urinary symptom scores. For patients with metastatic disease in the SWOG trial, intermittent ADT was associated with better erectile function and mental health, but the survival results were inconclusive.

Regardless of whether intermittent or continuous ADT is chosen for an individual patient based on the principles discussed herein, patients (and their partners) must be educated about the side effects of ADT and strategies to mitigate these effects. After 7 months of ADT, the extent to which the patient/couple is affected by ADT will be apparent. At that point, the advantage of using GnRH analogs or antagonists for ADT (over an orchiectomy) is that, should concerns about quality of life or comorbidity for an individual patient outweigh survival concerns, ADT can be discontinued and delivered on an intermittent basis.

Several caveats should be mentioned. First, the results of the NCIC and SWOG trials cannot be extrapolated to other intermittent ADT regimens. Second, the PSA thresholds for retreatment on the intermittent arms of both trials may not be optimal, and perhaps PSADT would be a better indicator of when to retreat. Third, the magnitude of the quality-of-life benefits of intermittent ADT was likely underestimated because of the timing of the questionnaires and/or the ability of the questionnaires to capture meaningful benefit. Fourth, results from the ECOG E3805 trial of continuous ADT with or without 6 months of docetaxel were recently announced. Men with castration-sensitive disease had a 3-year survival rate of 69.0% with the addition of docetaxel versus 52.5% with ADT alone, and those with liver metastases, 4 or more bone lesions, or both had a 3-year survival of 63.4% and 43.9%, respectively.[17] These results will likely impact the future standard of care for at least some men with metastatic castration-

sensitive disease. Lastly, when using intermittent ADT, development of castration resistance requires switching to continuous ADT.

Until ongoing and future research better identifies subgroups of patients to facilitate a more individualized approach to ADT, lessons learned from the NCIC and SWOG trials can be useful when making treatment decisions about continuous or intermittent ADT.

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