Intermittent hormone therapy and its place in the contemporary endocrine treatment of prostate cancer

Author: Shaw, G.; Oliver, R.T.D.

Publication info: Surgical Oncology 18. 3 (2009): 275-82.

Abstract: Castration results in dangerous and disabling side effects. Deferred hormone therapy has been shown to be associated with decreased survival. Intermittent hormone therapy (IHT) was attempted initially to reduce morbidity of treating metastatic prostate cancer with stilboestrol. Preclinical work using castrate mice with hormone sensitive prostate tumours demonstrated that pulses of testosterone delayed the onset of androgen independent growth and PSA production in these mice. This led to development of clinical treatment protocols for use in phase II trials by a number of centres in a variety of clinical scenarios. These phase II trials demonstrated apparent safety of this approach, prompting several large scale RCTs. Thus far no difference in survival has been demonstrated between IHT and continuous hormone therapy despite large numbers and prolonged follow-up. Quality of life has been proven to improve with stopping hormone therapy. A recent meta-analysis and multivariate analysis of phase II studies provides a unique opportunity to identify features of the various published IHT protocols which engender treatment success and allow the following recommendations to be made which may guide the clinician in devising their own IHT protocol. A PSA nadir below 1 ng/ml has been shown to be the best determinant of when it is safe to stop treatment. It can be achieved after as little as three months in patients with local disease. Patients with metastatic disease should be treated for at least eight months. Restarting treatment when the PSA rises to 15 ng/ml prolongs survival. MAB or LHRH monotherapy should be the standard of care in all patients with possible exception of recurrent disease after radiotherapy or prostatectomy where anti-androgen monotherapy may be appropriate. Initial PSA and the level of the PSA nadir achieved enable definition of prostate cancer patients in whom this approach may define a subgroup of local disease patients in whom it may be safe to avoid radical therapy. Preclinical and clinical data from a phase II trial demonstrating that addition of finasteride prolongs the off treatment period and provide the impetus for a randomized controlled trial (RCT) to prove this.

Full text:

Reference author	Origin	N	Type of disease	Type of treatment	PSA nadir for adequate response	Restart PSA	% off at 2 years
Strum [29]	California, USA	53	L &A	MAB	<0.05	>5	13
Youssef [30]	Michigan, USA	104	L, R &A	MAB/mono	<4	>10	39
Malone [26]	Ottawa, Canada	86	L, R &A	MAB/mono	<4	>10	20
Grossfeld [22]	San Francisco, USA	53	L &R	MAB/mono	<4 if no prev. Rx	>10	36

<0.1 post RT/RP	Or >50% baseline	De La Taille [23]	Paris, France	160	L, R &A	MAB/mono	<1 no prev Rx
>10	11	<0.05 post RP	>4 post RP	<4 post RT	Goldenberg [24]	Vancouver, Canada	101
L, R &A	MAB/mono	<2	>10	17	>4 post RP	Spry [28]	Perth, Australia
239	L, R &A	MAB	Variable - all 9 months MAB	>20	31	Lane [25]	London U.K.
125	L, R &A	MAB/mono	<4	>20	30	Prapotnich [27]	Paris, France
411	L, R &A	MAB	<4	>20	40	Albrecht [21]	Europe

Table 1 - The origins, characteristics and basic protocol for IHT from the different contributing authors. (L = localised disease primary treatment, R = biochemical recurrence after RP/RT localised, A = advanced disease).

Localised disease N0/M0, no previous treatment (n = 517)	Biochemical recurrence after failed curative treatment, N0/M0 (n = 563)	Metastatic disease (n = 366)
Overall survival at 5 years	90%	86%
68%	Patients off treatment at 2 years	29%
33%	16%	Patients with AIPC at 5 years
10%	17%	41%

Table 2 - Outcome of IHT by patient group (data from [32] with permission).

Type of study	Number of patients (randomized arm a/arm b)	Stage	Follow-up	Difference in survival
Hering 2000 [36]	Single centre RCT	43 (18/25)	Advanced	48 months
No significant difference	EAU TULP 2002 [36]	Multicentre, randomized, parallel group study	282 (96/97)	Advanced
26-40 months	No significant difference	Yamanaka 2005 [36]	Multicentre RCT	215 (48/41)
Locally advanced	22.6 months	No significant difference	de Leval [40]	Open label, multicentre RCT
68 (33/35)	Advanced	30.8 months	No significant difference	SEUG [37,38]
Multicentre, RCT	625 (312/313)	Locally advanced/advanced	84 months	No significant difference

Table 3 - Summary of RCTs included in Cochrane review demonstrating no significant difference in survival between intermittent and continuous hormone therapy. Introduction Since Huggins et al. demonstrated that castration resulted in regression of prostate cancer, hormonal manipulation remains the mainstay of treatment

for those with significant disease in whom radical therapy is not possible. Surgical castration has largely been replaced by medical castration. Castration is associated with a profound side effect profile in the long term. This includes anaemia, osteoporosis, impotence, cognitive functional effects, gynaecomastia, muscle atrophy, depression, dyslipidaemias, weight gain (as part of metabolic syndrome) and generalized lethargy [1,2]. The first description of intermittent hormone therapy for prostate cancer was in the 1980s when Whitmore Jr. et al. first stopped stilboestrol therapy in advanced disease patients to alleviate side effects with minimal apparent detriment [3]. This prompted workers to attempt to model the situation in animals. Work by Noble on Nb mice with hormone sensitive tumours [4] preceded laboratory work by other workers from Canada which demonstrated that in mouse models of hormone sensitive prostate cancer, intermittent administration of testosterone to castrate animals conferred a survival advantage due to delay in the development of androgen independence. They hypothesised that effect is due to removal of the selection pressure for androgen independent stem cell clones [5,6]. A great deal of clinical work followed in both experimental and clinical carcinomas. It has been shown that apoptosis can be induced multiple times using successive cycles of androgen withdrawal and replacement. Intermittent versus deferred hormone therapy An alternative way of minimising the duration of castration is to defer hormone treatment. A systematic review of 2167 patients treated in 4 different RCTs [7-10] conducted in 2002 treated with early or deferred hormone therapy in the pre-PSA era demonstrated a benefit to early hormone treatment in terms of disease progression but not survival. The most recent analysis of the EORTC 30853 study data demonstrated a significant decrease in survival which the authors concluded was negated by the impaired quality of life seen with early hormone treatment [11]. An ideal solution would therefore seem to be one in which treatment can be started early and the adverse effects minimised. IHT is one such solution. Theoretical basis for use of IHT to delay androgen independence Following Noble's work on mice, Akakura et al. used androgen dependent Shionogi mouse mammary carcinoma to demonstrate that androgen independent stem cell clones seemed to adapt to low androgen environs [5,12]. Thereafter Sato et al. generated their own models of prostate cancer by inoculating (androgen dependent) LNCaP cells intraprostatically in SCID mice [13]. The animals were castrated when tumour had developed and the tumours were seen to regress. Pulses of testosterone were administered with corresponding increases in PSA followed by PSA decreases on stopping the testosterone. This cohort of mice was compared with control animals with similar LNCaP tumour allografts which were castrate but did not receive pulses of testosterone. The PSA level was used to monitor response. The animals that received the pulses of testosterone showed delayed onset of PSA rise despite castrate levels of testosterone (on average after 26 days in Continuous androgen suppression compared with 77 days in Intermittent androgen suppression). Androgen independent clones are able to avoid the induction of apoptosis and grow in the absence of testosterone through a number of adaptive mechanisms. These include promiscuity of the androgen receptor which can be activated by factors other than androgens [14], the receptor can also be transactivated through increased activity due to mutation or upregulation of alternative growth factor pathways including EGFR, Her2/neu, IGF-1 and TGF-b [15], upregulation of anti-apoptotic pathways including Bcl-2 can counteract pro-apoptotic signaling [16]. These mechanisms develop in combination. It is theorised that by removing the selection pressure promoting the adaptive mechanisms described above, those clones that are capable, revert to normal growth patterns, including reversion to the apoptotic response to low androgen conditions. The stage is then set for another tumour regression response. This delay in onset of androgen independent growth characteristics has been reproduced by others using similar models and forms the basis of the rationale for ongoing clinical work [17]. Approaches The principle of IHT is that when a predetermined PSA nadir is reached hormone treatment can be stopped. An example demonstrating PSA kinetics for a single patient is shown in Fig. 1. Treatment is restarted once the PSA rises to a predetermined level or when there is evidence of clinical progression. Approximately 95% of patients diagnosed with CaP can be expected to show a PSA response adequate to allow cessation of hormone therapy. This proportion decreases with each successive cycle of

hormone therapy. Those patients with the best prognosis self-select for a period off hormones. Those who fail to achieve an adequate nadir level have the poorest prognosis and require prolonged hormone therapy and consideration for second line hormone therapy and/or chemotherapy. Docetaxal based chemotherapy regimes have become the standard of care in those who are medically fit in hormone escaped prostate cancer [18]. Recent work has demonstrated that it is possible to reinduce hormone response behaviour in some patients using chemotherapy [19,20]. In this way a short period of hormone ablation and the resultant PSA response differentiates those with poor prognosis from those with indolent disease who require less intensive treatment perhaps even active monitoring. Over the past decade several different IHT protocols have been developed for use in a variety of clinical situations [21-30]. All of the included protocols are based on the use of MAB or monotherapy with LHRH analogue or anti-androgen alone. The protocols vary in the levels to which the PSA is forced down. Some groups treated for a set duration regardless of whether an adequate PSA response occurred rapidly. The level to which the PSA is allowed to rise before hormone treatment is restarted varied between groups whilst all recommence treatment on evidence of clinical progression. PSA is the marker used to monitor response in IHT protocols. PSA production is androgen dependent. Frequently studies using PSA as an outcome do not include data on testosterone levels. Interpretation of PSA levels in the absence of contemporaneous serum testosterone is of limited value. PSA is currently the best marker as its measurement is easy and universally available (despite differing assay protocols). A consistent rise in PSA despite castrate levels of androgen is considered to indicate the onset of androgen independent growth. PSA is also produced in response to inflammation in the prostate. Its production is non-cancer specific. The ideal marker would be prostate cancer specific. One such moiety is DD3PCA3 . This non-coding sequence of RNA is of as yet unknown function. It is produced in a highly specific fashion by prostate cancer cells. Its production is also androgen dependent [31]. At present DD3PCA3 is measured by RT-PCR in urine as a diagnostic aid after prostate massage. Its detection in serum has not yet been studied. It or another prostate cancer specific element which is produced in an androgen sensitive fashion may make a superior alternative to PSA monitoring in the future. Clinical studies - phase 2 cohort studies A number of cohort studies have been carried out. Ten clinical studies incorporating over 50 patients were the subject of a recent meta-analysis [32] and are summarized in Table 1. Overall the pooled data from phase two studies demonstrate the apparent safety of IHT. Table 2 demonstrates the outcomes in terms of time off hormone therapy, time to androgen independence and overall survival for three groups of patients; 1- those treated primarily with IHT with no radiological evidence of metastasis, 2- those treated with IHT for biochemical failure after an attempt at curative therapy in the absence of evidence of metastasis and finally 3- those treated with IHT for proven metastatic disease. The individual patient data from 1446 patients treated according to differing IHT protocols included in the pooled dataset for the meta-analysis provide a unique means to examine features of IHT protocols which confer treatment success. This allows the formation of hypotheses to be tested in RCTs in order to optimise medication type and treatment cycling parameters. The issue of what type of medication is optimal in continual therapy has been the subject of much debate. Similar questions are posed in intermittent hormone treatment. The meta-analysis demonstrates that use of anti-androgen monotherapy is associated with a poorer outcome, as assessed by the time to PSA relapse, androgen independent growth and death [32]. A possible exception is those patients with recurrence after radical therapy. Other workers have reported similar findings [33]. It would seem that anti-androgen monotherapy can be used safely in these patients and that anti-androgen monotherapy is associated with a less disabling side-effect profile in the younger patient (thought to be due to the fact that anti-androgens produce an elevation in circulating testosterone) [34] and given intermittently could overcome the increased cardiovascular risk in older patients seen when used continuously [35]. A rapid and complete PSA response indicates a good prognosis both in terms of the likely duration of time off treatment and overall survival. The meta-analysis demonstrated no benefit to prolonged hormone therapy after a good PSA response (nadir <1 ng/ml) (see Fig. 2a). This is the case except in the presence of metastases when treatment should be continued

for at least 8 months. The PSA threshold at which treatment is restarted is predictive of the development of AIPC and overall survival in those with metastatic disease. Patients in whom the PSA rises to over 15 have a 1.3× risk of developing AIPC and a relative risk of 1.6× for death (see Fig. 2b). Phase 3 randomized controlled trials A recent Cochrane review [36] included pooled data from 5 RCTs and concluded that there was no evidence for IHT over continuous hormone therapy in terms of survival. Disappointingly the authors seem to have somewhat missed the point i.e. in "primum non nocere " (a doctor's primary duty above all is to do no harm) as they then go on to state that IHT can therefore not be recommended out of a clinical trial context. Given the maturity of these phase 3 trials and the large numbers of men with both metastatic and locally advanced disease that have been treated with IHT (data summarized in Table 3) and the cumulating evidence for risks of long-term androgen ablation, the conclusion should be totally the opposite. The largest RCT reported to date showed, with 626 patients randomized and follow-up of 7 years, that a 3-month period of hormone treatment produced equivalent overall survival to continuous therapy, and allowed 29% of those randomized to the IHT arm to remain off treatment for 3 years [37,38]. Since no survival advantage for continuous therapy has been reported in any of the trials [39] the conclusion should be that no more than 3 months for patients with locally advanced disease and 8 months for those with metastatic disease should become standard of care until these randomized trials show survival advantage for patients treated for longer periods. This conclusion is reinforced by the findings from de Leval et al. [40] who demonstrated a statistically significant ($p = 0.0052$) decrease in the estimated rate of disease progression (7% versus 38.9%) in patients with advanced prostate cancer treated with intermittent versus continuous hormone therapy, despite a short follow-up of only 30.8 months. Fortunately there are an increasing number of patients still being recruited to ongoing trials comparing continuous versus intermittent therapy which will further add to the amount of knowledge we have of IHT as detailed quality of life and cancer outcome events are being measured [41]. 1) National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) PR.7 (now closed to accrual) - for patients without evidence of metastasis with biochemical failure following radiotherapy. Sample size is 1360 patients. Outcome measures include PSA kinetics as well as quality of life. 2) South Western Oncology Group SWOG 9346 (NCIC PR.8) coordinated by M. Hussein et al. for newly diagnosed metastatic prostate cancer. This group recently reported some early data on PSA normalization rates. 84% of 527 patients had their PSA fall to within the normal range during the induction (first) cycle. This was more likely to occur in men who had: a younger age, a lower initial PSA, no weight change, no bone pain, no visceral metastases or distant nodal metastases. 96% of men who's PSA normalized, did so within 180 days. It is planned that this study will involve 1500 patients [42]. 3) EC 507(33) coordinated by U. Tunn et al. (abstract presented at AUA 2003) - 184 patients with PSA relapse following radical prostatectomy randomized to intermittent versus continuous hormone therapy. Mean follow-up 24 months. No difference in time to progression has been detected to date. More than 90% of men in the intermittent group regained normal testosterone values during the off phase of treatment. Testosterone recovery and quality of life after cessation of HT A longstanding criticism of intermittent hormone therapy is that there is a delay in the return to normal testosterone levels once the medication is stopped after a period of hormone ablation. One group found that 9.45 mg buserelin subcutaneously suppresses serum testosterone below the castration limit for at least 6 months [43]. This effect is not reported consistently. Gulley et al. reported on 80 patients with median normalization of testosterone after 6 months of subcutaneous LHRH analogue was 16.6 weeks with DHT normalising after 14.9 weeks, with 90% of patients attaining a normal testosterone within 18 weeks [44]. This inconsistency clearly demonstrates the need for monitoring serum testosterone levels in trials of IHT. Of more importance than arbitrary serum testosterone measurements is the patients' well-being and whether this improves after treatment is stopped. A recent paper by Spry et al. studied quality of life using validated questionnaires (EORTC QLQ-C30 and prostate specific module QLQ-PR25 version 3.0) [28]. They analysed adverse effects to quality of life arising from hormone treatment in 250 men treated with 9 months of LHRH as part of an IHT protocol and found that these effects could recover with stopping androgen

suppression. They found that following treatment cessation, testosterone recovery was progressive and median time to eugonadal levels (10 ng/ml) was 9.3 months. Improvements from end of MAB to peak recovery were significant for emotional function, sexual function, fatigue, sleep and hot flushes. Holistic quality of life scores also returned to baseline in this period. Overall the results demonstrate that hormone therapy results in rapid development of severe side effects which can be abrogated by cessation of treatment with a return to pre-treatment quality of life in almost all men. Prolonging the off period in IHT 5-α-Reductase inhibitors are known to inhibit the conversion of testosterone to the more potent derivative dihydroxytestosterone. Agents include finasteride and the newer dual inhibitor dutasteride [45]. Finasteride is predominately used in benign prostatic hypertrophy though a large trial has demonstrated some use in preventing prostate cancer [46]. Use of finasteride in BPH has demonstrated that inhibition of 5-α-reductase brings about a 50% reduction in serum PSA levels [47]. The fact that PSA is lowered by these drugs and that restarting on treatment period in IHT protocols is prompted by a rise in PSA has generated some interest in the use of finasteride in this context. Hormone therapy for localised disease is usually only appropriate for selected patients in whom radical treatment is not possible, when radical treatment has failed, when PSA is very high despite a negative bone scan or in whom life expectancy is short. Leibowitz et al. report a phase 2 study of 110 patients with localised T1-4 N0 M0 disease made use of a particular IHT protocol which the authors refer to as combined androgen blockade. This consists of a year of MAB plus finasteride followed by maintenance with finasteride only. This approach has been complimented by preclinical data where finasteride combined with pulsed testosterone administration in castrate mice with LNCaP xenograft defers the need to restart hormones due to PSA rise and increases survival [48]. In addition Scholz et al. performed a retrospective review of 101 men treated with finasteride during the off period in IHT and found that addition of finasteride doubled off treatment period [49]. The second meeting of the ISICAP group in Vancouver in March 2006 entailed a presentation by Klotz of an RCT protocol which is now actively recruiting to evaluate the use of dutasteride in prolonging the off period. It is unfortunate that this study is using nine months of intermittent therapy and is not addressing the issue of whether 5-α-reductase inhibition during induction maintenance or both is necessary. The use of IHT in patients with localised disease who are unsuitable for radical treatment might allow identification of a low risk group in whom a very low PSA nadir was achieved after only a short period of androgen ablation. Thereafter only those with a poor response might need to undergo further treatment. Conclusion: the place of IHT in the contemporary endocrine treatment of prostate cancer - practical advice for the clinician Phase II studies of IHT demonstrate its safety of treatment in terms of durability of maintenance of androgen-sensitivity and overall survival compared to historic controls as well as improved toxicity profile. In addition there is a growing body of phase III evidence that IHT in both locally advanced and metastatic disease produces equivalent survival to continuous hormone therapy with follow-up as long as eight years. In these studies there is also demonstrable initial improvement of quality of life and confirmation that there is a subgroup of about a third who can have prolonged survival off treatment with recovery of testosterone. Despite these data, the current view of opinion leaders is that intermittent hormone therapy should not be a standard of care [41,50]. An alternate view accepted in the recently published UK NICE guidelines is that the increasing catalogue of side effects from long-term androgen deprivation merits its acceptance as an alternate at this stage (albeit with the proviso that patients are counseled regarding the lack of long-term evidence of effectiveness) [51]. This attitude is enhanced by increasing data showing that low serum testosterone is associated with higher grade prostate cancer [52] and increased neuroendocrine differentiation [53]. These suggest that long-term hormone ablation results in increased occurrence of features associated with poor prognosis and is in keeping with theory of clonal selection of resistant clones through androgen ablation. This may be due to higher levels of 5-α-reductase type 1 and type 2 in localised high grade prostate cancer when compared with low grade [54]. The short-term safety of a short course of hormone ablation and increasing evidence demonstrating over-treatment of early disease suggest that patients should be made aware of the option. The diagnosis of prostate cancer is frequently

followed by a period of contemplation of the treatment options. This period might be used to define a patient's prognosis by identifying those with a poor response to a course of hormone ablation (although this is not recommended by guidelines). The counterargument to this is that atrophy of the gland is associated with fibrosis rendering surgical treatment more technically demanding [55]. The suggestion of stopping hormones is certainly justifiable in patients who were suffering with side effects from hormonal treatment. The evidence suggests that it is safe to stop treatment after as little as 3 months LHRH if a PSA nadir of <2 is reached, except in the presence of radiologically proven metastatic disease when treatment should continue for at least 8 months. PSA and testosterone levels should be monitored every three months and treatment restarted when the PSA level reaches 15. In the authors' experience the difficulty is in stopping medication at a stage when the PSA is low. The action is contrary to the usual practice of maintaining a treatment which would seem to be working. Commencement of a period of hormone ablation of a duration pre-arranged in discussion between clinician and patient, provided a predetermined PSA nadir is achieved, may be an easier way to establish this practice. Conflict of interest statement None. Acknowledgements This work was undertaken with support from the Orchid Cancer Appeal. References Berruti A, Tucci M, Terrone C, Gorzegno G, Scarpa RM, Angeli A: Background to and management of treatment-related bone loss in prostate cancer 10 . Drugs Aging 19 (12): 899-910, 2002. Salminen EK, Portin RI, Koskinen A, Helenius H, Nurmi M: Associations between serum testosterone fall and cognitive function in prostate cancer patients 96 . Clin Cancer Res 10 (22): 7575-7582, 2004. Klotz LH, Herr HW, Morse MJ, Whitmore WF Jr.: Intermittent endocrine therapy for advanced prostate cancer 33 . Cancer 58 (11): 2546-2550, 1986. Noble RL: Hormonal control of growth and progression in tumors of Nb rats and a theory of action . Cancer Res 37 (1): 82-94, 1977. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D: Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma 54 . Cancer Res 50 (8): 2275-2282, 1990. Sato N, Gleave ME, Bruchovsky N, Rennie PS, Goldenberg SL, Lange PH: Intermittent androgen suppression delays progression to androgen-independent regulation of prostate-specific antigen gene in the LNCaP prostate tumour model 20 . J Steroid Biochem Mol Biol 58 (2): 139-146, 1996. Byar DP: Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate . Cancer 32 (5): 1126-1130, 1973. Jordan WP Jr., Blackard CE, Byar DP: Reconsideration of orchiectomy in the treatment of advanced prostatic carcinoma . South Med J 70 (12): 1411-1413, 1977. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D: Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer . N Engl J Med 341 (24): 1781-1788, 1999 Dec 9. The Medical Research Council Prostate Cancer Working Party Investigators, G., immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial . BJU Int 136 235- 1997. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D: Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891 . J Clin Oncol 24 (12): 1868-1876, 2006 Apr 20. Akakura K, Bruchovsky N, Goldenberg SL, Rennie PS, Buckley AR, Sullivan LD: Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen 21 . Cancer 71 (9): 2782-2790, 1993. Sato N, Sadar MD, Bruchovsky N, Saatcioglu F, Rennie PS, Sato S: Androgenic induction of prostate-specific antigen gene is repressed by protein-protein interaction between the androgen receptor and AP-1/c-Jun in the human prostate cancer cell line LNCaP 66 . J Biol Chem 272 (28): 17485-17494, 1997. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK: Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer 34 . N Engl J Med 332 (21): 1393-1398, 1995. Craft N, Shostak Y, Carey M, Sawyers CL: A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase . Nat Med 5 (3): 280-285, 1999. Raffo AJ, Perlman H, Chen MW, Day ML, Streitman JS, Buttyan R: Overexpression of bcl-2 protects prostate cancer cells from apoptosis in vitro and confers resistance to androgen depletion in vivo . Cancer Res 55 (19): 4438-4445,

1995. Buhler KR, Santucci RA, Royai RA, Whitney SC, Vessella RL, Lange PH: Intermittent androgen suppression in the LuCaP 23.12 prostate cancer xenograft model 24 . Prostate 43 (1): 63-70, 2000. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer . N Engl J Med 351 (15): 1502-1512, 2004. Shamash J, Dancey G, Barlow C, Wilson P, Ansell W, Oliver RT: Chlorambucil and lomustine (CL56) in absolute hormone refractory prostate cancer: re-induction of endocrine sensitivity an unexpected finding . Br J Cancer 92 (1): 36-40, 2005. Shamash J, Davies A, Ansell W, McFaul S, Wilson P, Oliver T: A phase II study investigating the re-induction of endocrine sensitivity following chemotherapy in androgen-independent prostate cancer . Br J Cancer 98 (1): 22-24, 2008. Albrecht W, Collette L, Fava C, Kariakine OB, Whelan P, Studer UE: Intermittent maximal androgen blockade in patients with metastatic prostate cancer: an EORTC feasibility study 5 . Eur Urol 44 (5): 505-511, 2003. Grossfeld GD, Small EJ, Carroll PR: Intermittent androgen deprivation for clinically localized prostate cancer: initial experience . Urology 51 (1): 137-144, 1998. De La Taille A, Zerbib M, Conquy S, Amsellem-Ouazana D, Thiounn N, Flam TA: Intermittent androgen suppression in patients with prostate cancer 39 . BJU Int 91 (1): 18-22, 2003. Goldenberg SL, Bruchovsky N, Gleave ME, Sullivan LD, Akakura K: Intermittent androgen suppression in the treatment of prostate cancer: a preliminary report 30 . Urology 45 (5): 839-844, 1995. Lane TM, Ansell W, Farrugia D, Wilson P, Williams G, Chinegwundoh F: Long-term outcomes in patients with prostate cancer managed with intermittent androgen suppression 35 . Urol Int 73 (2): 117-122, 2004. Malone S, Perry G, Segal R, Dahrouge S, Crook J: Long-term side-effects of intermittent androgen suppression therapy in prostate cancer: results of a phase II study 134 . BJU Int 96 (4): 514-520, 2005. Prapotnich D, Fizazi K, Escudier B, Mombet A, Cathala N, Vallancien G: A 10-year clinical experience with intermittent hormonal therapy for prostate cancer 43 . Eur Urol 43 (3): 233-239, 2003. Spry NA, Kristjanson L, Hooton B, Hayden L, Neerhut G, Gurney H: Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer . Eur J Cancer 42 (8): 1083-1092, 2006. Strum SB, Scholz MC, McDermed JE: Intermittent androgen deprivation in prostate cancer patients: factors predictive of prolonged time off therapy . Oncologist 5 (1): 45-52, 2000. Youssef E, Tekyi-Mensah S, Hart K, Bolton S, Forman J: Intermittent androgen deprivation for patients with recurrent/metastatic prostate cancer 7 . Am J Clin Oncol 26 (5): e119-e123, 2003. Shaw G, Purkiss T, Oliver RT, Prowse DM: Re: Christine McKillop. Interview with Jack Schalken: PCA3 and its use as a diagnostic test in prostate cancer . Eur Urol 50 153-154, 2006. Shaw GL, Wilson P, Cuzick J, Prowse DM, Goldenberg SL, Spry NA: 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 99 (5): 1056-1065, 2007. Peyromaure M, Delongchamps NB, Debre B, Zerbib M: Intermittent androgen deprivation for biologic recurrence after radical prostatectomy: long-term experience 106 . Urology 65 (4): 724-729, 2005. Gillatt D: Antiandrogen treatments in locally advanced prostate cancer: are they all the same? . J Cancer Res Clin Oncol 132 (Suppl. 1): S17-S26, 2006 Aug. Iversen P, Roder MA: The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer . Expert Rev Anticancer Ther 8 (3): 361-369, 2008. Conti PD, Atallah AN, Arruda H, Soares BG, El Dib RP, Wilt TJ: Intermittent versus continuous androgen suppression for prostatic cancer . Cochrane Database Syst Rev (4): 2007. Calais Da Silva F, Bono A: Phase III study of Intermittent MAB versus continuous MAB. International co-operative study (abstract). Whelan P, Brausi M, Queimadelos M, Portilho J . Kirkali Z. J Urol 173 ((4) supp): 309- 2005. Tunn U: The current status of intermittent androgen deprivation (IAD) therapy for prostate cancer: putting IAD under the spotlight . BJU Int 99 (Suppl. 1): 19-22, 2007. de Leval J, Boca P, Yousef E, Nicolas H, Jeukenne M, Seidel L: Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone-naive prostate cancer: results of a prospective randomized multicenter trial 107 . Clin Prostate Cancer 1 (3): 163-171, 2002. Boccon-Gibod L, Hammerer P, Madersbacher S, Mottet N, Prayer-Galetti T, Tunn U: The role of intermittent androgen deprivation in prostate cancer . BJU Int 100 (4): 738-743, 2007. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED: 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 24 (24): 3984-3990, 2006 Aug 20. Pettersson B, Varenhorst E, Petas A, Sandow J: Duration of testosterone suppression after a 9.45 mg implant of the GnRH-analogue buserelin in patients with localised carcinoma of the prostate a 12-month follow-up study . Eur Urol 50 (3): 483-489, 2006 Sep. Gulley JL, Figg WD, Steinberg SM, Carter J, Sartor O, Higano CS: A prospective analysis of the time to normalization of serum androgens following 6 months of androgen deprivation therapy in patients on a randomized phase III clinical trial using limited hormonal therapy 133 . J Urol 173 (5): 1567-1571, 2005. Andriole GL, Humphrey P, Ray P, Gleave ME, Trachtenberg J, Thomas LN: Effect of the dual 5alpha-reductase inhibitor dutasteride on markers of tumor regression in prostate cancer . J Urol 172 (3): 915-919, 2004 Sep. Thompson IM, Klein EA, Lippman SM, Coltman CA, Djavan B: Prevention of prostate cancer with finasteride: US/European perspective 72 . Eur Urol 44 (6): 650-655, 2003. Handel LN, Agarwal S, Schiff SF, Kelty PJ, Cohen SI: Can effect of finasteride on prostate-specific antigen be used to decrease repeat prostate biopsy? . Urology 68 (6): 1220-1223, 2006 Dec. Eggener SE, Stern JA, Jain PM, Oram S, Ai J, Cai X: Enhancement of intermittent androgen ablation by "off-cycle" maintenance with finasteride in LNCaP prostate cancer xenograft model . Prostate 66 (5): 495-502, 2006 April 1. Scholz MC, Jennrich RI, Strum SB, Johnson HJ, Guess BW, Lam RY: Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period . J Urol 175 (5): 1673-1678, 2006 May. Bhandari MS, Crook J, Hussain M: Should intermittent androgen deprivation be used in routine clinical practice? . J Clin Oncol 23 (32): 8212-8218, 2005. Schatzl G, Madersbacher S, Thurridl T, Waldmuller J, Kramer G, Haitel A: High-grade prostate cancer is associated with low serum testosterone levels . Prostate 47 (1): 52-58, 2001. Wafa LA, Palmer J, Fazli L, Hurtado-Coll A, Bell RH, Nelson CC: Comprehensive expression analysis of L-dopa decarboxylase and established neuroendocrine markers in neoadjuvant hormone-treated versus varying Gleason grade prostate tumors . Hum Pathol 38 (1): 161-170, 2007. Gleave M, Qian J, Andreou C, Pommerville P, Chin J, Casey R: The effects of the dual 5alpha-reductase inhibitor dutasteride on localized prostate cancer-results from a 4-month pre-radical prostatectomy study . Prostate 66 (15): 1674-1685, 2006. Van Poppel H, Ameye F, Oyen R, Van DV, Baert L: Neo-adjuvant hormonotherapy does not facilitate radical prostatectomy . Acta Urol Belg 60 (3): 73-82, 1992.

Subject: Prostate cancer; Hormone replacement therapy; Menopause; Androgens

MeSH: Animals, Clinical Trials as Topic, Humans, Male, Mice, Antineoplastic Agents, Hormonal -- therapeutic use (major), Neoplasms, Hormone-Dependent -- drug therapy (major), Prostatic Neoplasms -- drug; therapy (major)

Substance: Antineoplastic Agents, Hormonal

Identifier / keyword: Prostate cancer, Intermittent, Quality of life, Hormone therapy, Androgen ablation, Androgen suppression

Publication title: Surgical Oncology

Volume: 18

Issue: 3

Pages: 275-82

Publication year: 2009

Publication date: 2009

Year: 2009

Publisher: Elsevier Limited

Place of publication: Oxford

Country of publication: United States

Publication subject: MEDICAL SCIENCES--ONCOLOGY, MEDICAL SCIENCES--SURGERY

ISSN: 09607404

Source type: Scholarly Journals

Language of publication: English

Document type: EDB, Review, Journal Article

DOI: http://dx.doi.org/10.1016/j.suronc.2009.02.003

Accession number: 19269165

ProQuest document ID: 1035160160

Document URL: http://search.proquest.com/docview/1035160160?accountid=32970

Last updated: 2013-02-21

Database: ProQuest Research Library
