Supplementary data: Maximal testosterone suppression in the management of recurrent and metastatic prostate cancer

Laurence Klotz, MD, FRCSC;[1] Rodney H. Breau, MD, MSc, FRCSC;[2] Loretta L. Collins, PhD;[3] Martin E. Gleave, MD, FRCSC, FACS;[4] Tom Pickles, MD, FRCPC;[5] Frederic Pouliot, MD, PhD, FRCSC;[6] Fred Saad, MD, FRCSC[7]

[1]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]Kaleidoscope Strategic, Toronto, ON, Canada; [4]Vancouver Prostate Centre, Vancouver, BC, Canada; [5]British Colombia Cancer Agency, Vancouver, BC, Canada; [6]Hôtel-Dieu de Québec, Quebec City, QC, Canada; [7]Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

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Table 2. Retrospective studies of androgen-deprivation therapy outcomes by testosterone level

Study type N Setting	ADT regimen(s)	T level	Time to PSA progression (months)	PFS (months) HR (95% CI)	OS (months) HR (95% CI) or (range)	Other results
Pickles 2012[31] Database review 2196 L, LA	Curative RT Adjuvant LHRHA therapy	>1.1 nmol/l[a]	NR	NR	NR	• Rate of T breakthrough[b] with increase to >1.1 nmol/l was 6.6% per patient course and 5.4% per LHRHA injection, and rate with increase to >1.7 nmol/l was 3.4% per patient course and 2.2% per LHRHA injection. • Repeated breakthroughs occurred in 16% of patients. • Younger men were more liable to breakthroughs (p<0.001). • Early PSA kinetic surrogates of cancer control were inferior in those with breakthroughs. • Post-treatment PSA nadir was also higher in those with breakthroughs: 0.02 ng/ml for those without a breakthrough, compared with 0.04 ng/ml for testosterone >1.1 nmol/l or >1.7 nmol/l (p=0.008 and p=0.003, respectively).
		>1.7 nmol/l[a]				
Kamada 2015[26] Multicentre 225 L, LA & Met	CAB with LHRH agonists (leuprorelin goserelin), LHRH antagonists (degarelix) or surgical castration and antiandrogens[c]	<0.7 nmol/l[d]	NR	16.3 p=0.1163[e]	68.3 p<0.0014[e]	• For OS on univariate analysis, NT <0.6 nmol/l (p=0.0190), <0.7 nmol/l (p=0.0020), and <1.1 nmol/l (p=0.0146) were significant together with other clinical factors. • NT <0.3 and <0.4 nmol/l were not significant. • Multivariate analysis showed that NT <0.7 nmol/l was a significant prognostic and predictive factor for OS (p=0.0048). • NT <0.7 nmol/l showed the most significant difference for OS (p<0.0001) compared to NT at 6 mos <0.7 nmol/l (p=0.0479) or NT <0.3 nmol/l (p=0.1031).
		≥0.7 nmol/l[d]		11.0	28.3	
Perachino 2010[28] Single-centre 129 Met	Goserelin 10.8 mg every 12 wks	1.4 nmol/l (6 mo mean)	NR	NR	NR (CSS) 1.333 (1.053–1.687) (p<0.05)[f]	• Higher T level at 6 mos increases the risk of death by 1.33 times (95% CI 1.053–1.687). • There was a continuous relationship between testosterone level and CSS: the pretreatment Gleason score and 6-mo PSA level being equal, the lower the 6-mo testosterone level, the longer the survival.

Table 2. (cont'd). Retrospective studies of androgen-deprivation therapy outcomes by testosterone level

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Shiota 2016[24] Single-centre 96 LA & Met	Surgical castration or medical castration using a LHRH agonist (goserelin acetate or leuprorelin acetate) and/or antiandrogen (bicalutamide, flutamide or chlormadinone acetate) continuously	0.1 nmol/l (2.0–4.0 ng/dl)[g] (Q1; n=24)	NR	NR p=0.70	95.4[h] p=0.014[i]	• ST levels were significantly associated with OS, but not PFS (univariate analysis). • For survival rate from progression, the ST Q1 group had better prognosis, compared with that of the Q2, Q3, and Q4 groups (p=0.037) and the Q2–Q4 group (p=0.0044).
		0.1–2.6 nmol/l (4.3–76 ng/dl)[g] (Q2–4; n=72)		NR	NR	
Morote 2007[30] Single-centre 73[j] L, LA	LHRHA every 3 mos Bicalutamide 50 mg/day 2 wks prior to first LHRHA administration	All measurements <0.7 nmol/l (n=32)	NR	106[k]	NR	• Rates of T breakthroughb with T level 0.7–1.7 nmol/l were observed in 31.5% of patients, and increases >1.7 nmol/l were observed in the remaining 24.7%. • The lowest serum T threshold with clinical impact was 1.1 nmol/l; p=0.0258. • Patients with all 3 determinations of serum T <1.1 nmol/l had a mean survival free of androgen-independent progression of 137 mos vs. 88 mos for those with any breakthrough increase >1.1 nmol/l; p<0.03.
		Any increase between 0.7–1.7 nmol/l (n=23)		90[k]		
		Any increase >1.7 nmol/l (n=18)		72[k]		
Yasuda 2015[25] Retrospective 69 Met	LHRHAs leuprolide acetate (n=28) or goserelin acetate (n=41) Bicalutamide 80 mg/day 2 wks before first LHRHA administration, and continued with CAB therapy	<0.7 nmol/l[l] (n=57)	15.5[h] p=0.66	NR	NYR p=0.17 NYR (CSS) p=0.29	• No threshold (0. 5, 0.7, or 1.1 nmol/l) of median T level showed a significant relation with TTP, CSS, or OS. • Mean maximum T level of each patient during treatment was 0.7 nmol/l (median 0.6 nmol/l). • Mean minimum T level of each patient during treatment was 0.4 nnmol/l (median 0.4 nmol/l).

[a]Breakthrough level; [b]increase in serum T >0.7 nmol/l was considered a breakthrough response; [c]bicalutamide, flutamide, or chlormadinone; [d]nadir; [e]Wilcox on signed rank test; [f]continuous relationship between testosterone level and CSS; increased risk of death with higher testosterone level at 6 mos; [g]mean; [h]estimated from plot; [i]ST Q1 showed improved OS vs. ST Q2–4; [j]28 patients continued treatment with bicalutamide for maximal androgen blockade; [k]mean androgen-independent progression-free survival; [l]median. ADT: androgen-deprivation therapy; CAB: combined androgen blockade; CI: confidence interval; CSS: cause (cancer)-specific survival; HR: hazard ratio; L: localized; LA: locally advanced; LHRH(A): luteinizing hormone-releasing hormone (agonist); Met: metastatic; mo(s): month(s); N or n: number of patients; NR: not reported; NT: nadir testosterone; NYR: not yet reached; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; QX: quartile X; RT: radiotherapy; ST: serum testosterone; T: testosterone; TTP: time to progression; wk(s): weeks.