

Post-transplant complications

Management of erectile dysfunction by combination therapy with testosterone and sildenafil in recipients of high-dose therapy for haematological malignancies

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Summary:

Erectile dysfunction (ED) is a well recognised complication of bone marrow transplantation, which affects quality of life in adult patients. Although the major contributory factors include hypogonadism and psychogenic factors, the best treatment still remains to be established due to the complex aetiopathology of the condition. Here, we report our preliminary results in eight patients treated with testosterone replacement therapy and sildenafil. We studied eight male recipients of BMT aged 22–58 years, presenting with clinical features of hypogonadism, ED, diminished libido and ejaculatory disorders. ED was assessed clinically and by colour flow Doppler studies of the cavernosal vessels. Testicular function was assessed by testicular volume, FSH, LH and testosterone (T) measurements. Erectile performance, libido and ejaculatory function were determined by a structured interview. Patients had severe primary hypogonadism as evidenced by low mean testicular volume, elevated gonadotrophins and low normal mean testosterone levels compared with controls. All had Leydig cell insufficiency (LCI) with or without frank serum testosterone insufficiency. All except one had cavernosal arterial insufficiency. All patients received intramuscular injections of testosterone cypionate (250 mg 4 weekly) for 6 months and 50–100 mg of sildenafil orally, one to two times per week. All patients responded favourably as substantiated from the NIH consensus criteria. Our preliminary results suggest that this combined therapy is a safe and effective therapeutic approach in recipients of high-dose therapy presenting with ED after transplant.

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Introduction

Erectile dysfunction (ED) is a well recognised complication of high-dose therapy and haemopoietic stem cell transplantation and contributory factors include hypogonadism^{1,2} and psychogenic factors.^{3,4} A recent study of patients with severe erectile dysfunction following melphalan and total body irradiation (TBI) and autologous haemopoietic stem cell transplantation also showed that cavernosal arterial insufficiency is a significant factor.⁵ All five of the patients that we studied had subnormal penile Doppler blood flow rates as well as Leydig cell insufficiency. Subsequently, we reported⁶ cavernosal arterial insufficiency in recipients of marrow/stem cell transplant following high-dose chemotherapy without TBI.

In patients with such combined deficiencies the ideal treatment is unknown. We hypothesised that combination therapy with testosterone replacement and sildenafil would be a logical option to correct the hormonal deficiency and to vasodilate appropriately stimulated blood vessels, respectively. The encouraging preliminary results reported here with this strategy encourage further trials and use of this therapy in males with chemo/radiotherapy-induced sexual dysfunction.

Patients and methods

Eight male recipients of high-dose chemotherapy and stem cell transplantation aged 22–58 years, who complained of moderate or severe erectile dysfunction and inability to have sexual intercourse, were studied 2–24 months after high-dose therapy. Five patients with lymphoma (three with Hodgkin's lymphoma and two with non-Hodgkin's lymphoma) had received treatment with BEAM (carmustine 300 mg/m² on day –6, etoposide 200 mg/m² on days –5 to –2, cytarabine 200 mg/m² on days –5 to –2 and melphalan 140 mg/m² on day –1) and autologous peripheral blood stem cells (PBSC). One patient with Hodgkin's disease had received a fludarabine-based (CAMPATH-1H 20 mg/day on days –8 to –4, fludarabine 30 mg/m² on days –7 to –3 and melphalan 140 mg/m² on

day -2) non-myeloablative stem cell sibling allograft. Two further patients (one with myelodysplastic syndrome and the other with acute myeloid leukaemia) had received a cyclophosphamide/TBI (cyclophosphamide 60 mg/kg for 2 days and fractionated TBI at a dose of 12 cGy) sibling allogeneic bone marrow transplant.

Evaluation of sexual dysfunction

The extent of erectile dysfunction, reduction in libido, ejaculatory function and overall sexual performance were determined by interview. ED was graded using previously published criteria as follows: severe erectile dysfunction with no evidence of erection was scored as grade 0, tumescence without rigidity as grade I, partial erection inadequate for a successful penetration as grade II, and full rigidity as grade III.⁶ Libido and ejaculation were defined according to Master's and Johnson's criteria.³

Endocrine assessment

Hypogonadism was determined by evaluating germ cell as well as the Leydig cell compartments from the endocrine profile, which consisted of FSH, LH, % free and total testosterone. Thyroid (T) function tests (free thyroxine and TSH data not given), and adrenal androgens (dehydroepiandrosterone and androstenedione) were also measured. All hormones were assayed by standard radioimmunoassay using double antibody techniques. This was undertaken according to our previously published protocol.⁶ Testicular volume was assessed clinically by using Prader's orchidometer and confirmed by testicular ultrasound. In the event of discrepancy, the ultrasonic measurement was used.

Doppler studies of the penile cavernosal system

Prostatic ultrasound was performed to exclude hyperplasia or adenoma. Colour flow Doppler was undertaken to assess the haemodynamic function of the penis after injection of the vasoactive agent 20 µg PGE1. A peak systolic velocity (PSV) of <30 cm/s was defined as an index of vascular insufficiency.⁶ Response to the intracavernosal injection was graded 0–III as above.

Results

The characteristics of the eight patients in this study, and their hormonal and penile blood measurements prior to the therapeutic trial, are shown in Table 1.

All patients presented with grade I or II ED, 6/8 had diminished libido and 5/8 had premature ejaculation. All patients had cavernosal arteriogenic insufficiency. All except one patient had germ cell insufficiency as evidenced from elevated FSH and diminished testicular volumes compared with the control subjects. Four patients also had LCI as evidenced from elevated LH levels.

In addition, all except one patient had low adrenal androgen (dehydroepiandrosterone, DHEAS) levels. Patients 2 and 4 also had low androstenedione (AS) levels (Table 2).

All patients received a therapeutic trial for 6 months of

testosterone ester (250 mg i.m. monthly testosterone cypionate, TRT), together with 50–100 mg of sildenafil orally, once or twice weekly. An assessment was made at 3 months and again at 6 months. Therapeutic response was considered good if the patient could maintain an erection adequate for successful sexual intercourse in line with the NIH consensus criteria.⁷

Following a therapeutic trial of testosterone cypionate and sildenafil all eight patients had had sufficient improvement to be able to successfully complete sexual intercourse. All except one (patient 2) had correction of premature ejaculation. As a group, all patients showed a marked improvement in total and bioactive % free T levels.

Discussion

ED is a distressing problem in male BMT recipients. In recent years it has become apparent that ED is multifactorial in origin and both organic and psychogenic factors may be held responsible. However, in contradistinction to the conventional view where psychogenic factors are largely held responsible for sexual dysfunction in cancer patients, our data suggest the dual pathology of hypogonadism and cavernosal arterial insufficiency to be the key contributors to ED. We suggest that psychogenic factors may have played a permissive role in the aetiology of ED in these patients.

Undoubtedly, the commonest endocrine cause was primary hypogonadism, with or without Leydig cell insufficiency (LCI). Although we and others^{8–10} have reported Leydig cell insufficiency in patients treated by chemoradiotherapy, diminished adrenal androgen levels have not been reported before in patients presenting with features of hypogonadism. It is not difficult to understand the effects of LCI in sexual dysfunction in these patients as many had diminished libido and absence of nocturnal tumescence which has been reported in other patients with sexual dysfunction.⁹

Penile arterial insufficiency is a major cause of ED in our patients, as has been previously reported by us. Since erection is primarily a vasculogenic event controlled by neurohumoral regulation at the central and peripheral levels,¹¹ correction of penile vasculopathy by a vasodilator seems to be a logical option. The selective phosphodiesterase (PDE5) inhibitor sildenafil potentiates the nitric oxide pathway via the C-GAMP mechanism.¹² The main advantage of sildenafil is that it treats the symptoms of erectile dysfunction irrespective of the cause (psychogenic or organic). This is especially useful in BMT recipients, where both organic and psychogenic factors are responsible for ED.

One of the major limitations of sildenafil is its inability to affect sexual desire as it only works on the sexually stimulated penis.¹³ Thus, sildenafil monotherapy is likely to be less effective in BMT patients who have diminished libido and impaired nocturnal tumescence due to LCI. In addition, testosterone can improve energy, drive and correct generalised symptoms of depression and fatigue as well as improving psychosexual esteem and cognitive function in patients with hypogonadism.^{14,15} Thus, TRT is a logical

Table 1 Patient characteristics

Patient No.	Disease	Age	ED	Libido	Ejaculation	Testicular volume	
						R	L
1	HD	37	I	L	P	4	6
2	NHL	57	I	L	N	9	10
3	NHL	45	I	N	P	8	8
4	HD	22	II	L	P	4	4
5	HD	58	II	L	P	4	5
6	HD	25	II	L	P	8	9
7	MDS	50	II	L	N	10	8
8	AML controls	34	I	N	N	8	8
						15–25	

HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; MDS = myelodysplastic syndrome; AML = acute myeloid leukaemia; ED = erectile dysfunction; L = low; N = normal; P = premature; R = right; L = left.

Table 2 Endocrine profile pre- and post transplantation

Patient No.	PDF		FSH	FSH	LH	LH	DHEAS	AS	SHBG	E2	Total testosterone		% free testosterone	
	cm/s		pre Tx	Post Tx	IU/l	IU/l	($\mu\text{mol/l}$)	($\mu\text{mol/l}$)	(nmol/l)	(pmol/l)	Pre Tx	Post Tx	Pre Tx	Post Tx
	R	L	IU/l	IU/l	Pre Tx									
1	25	50	8.6	14	4.2	10.2	1.7	4.3	24	80	14	18	1.7	2.0
2	20	20	10	38.1	4.6	10.3	3.4	2.4	46	128	17.9	49.3	1.37	2.0
3	16	16	10.8	17	4	5.1	2.7	5.4	33	84	8.37	25.6	0.9	1.57
4	16	16	10.8	17	4	6.6	1.8	2.2	42	80	16.7	20.2	1.8	2.0
5	25	25	12.6	18.4	4	7.7	2.0	4.2	28	60	12.6	15.4	1.8	1.94
6	25	25	12	11.3	5	13.7	8.6	7.9	34	176	15.9	18.4	1.5	5.8
7	19	20	4	7	2	3	2.4	5.2	34	120	12.7	15.8	1.54	1.8
8	25	25	8.8	20	3	18.40	1.4	3.8	45	100	11.8	20.2	1.58	2.06
Controls	>30		2–10	2–10	2–20	2–10	4–10	4–10	10–45	30–150	10–25		1.24–3.4%	

PDF = penile Doppler flow; Tx = transplantation; FSH = follicle stimulating hormone; LH = leuteinising hormone; DHEAS = dehydroepiandrosterone, AS = androstenedione; SHBG = sex hormone binding globulin; E2 = oestradiol.

combination with sildenafil in these patients who have dual pathology. Recent data suggest that testosterone is a smooth muscle relaxant for the penile vessels¹⁶ which is likely to potentiate the action of sildenafil. Although no properly conducted study is available to provide hard scientific data on the efficacy of combination therapy of TRT with sildenafil, improvement in libido may increase erectile performance, thereby self-correcting borderline testosterone insufficiency. This is backed up by the evidence that lack of sexual activity from ED is associated with a reversible reduction in serum testosterone.¹⁷ Thus, sildenafil may augment the efficacy of TRT.

In summary, this is the first report where BMT recipients presenting with ED for combined LCI and penile arteriopathy were treated effectively with TRT and sildenafil and were able to obtain physiological and pharmacologically active erections sufficient for satisfactory sexual intercourse. Due to the potential cardiotoxicity of sildenafil and potential risk of TRT on prostatic hyperplasia, we recommend a comprehensive work up of cardiac status (in cardiac risk patients) and prostatic ultrasound prior to initiation of therapy. Also, long-term follow up of these patients with yearly ECG monitoring, prostate-specific antigen (PSA) assay and prostatic ultrasound may be rec-

ommended¹⁸ since these patients are at increased risk for development of a second cancer.

References

- Kassabian VS. Erectile dysfunction in the cancer patient *Cancer Control* 2000; **7**: 177–80.
- Costabile RA. Cancer and male sexual dysfunction. *Oncology* 2000; **14**: 195–200, 203; discussion 203–205.
- Masters WH, Johnson VE. Principles of the new sex therapy. *Am J Psychiatry* 1976; **133**: 548–554.
- Kaplan HS, Kohl RN, Pomeroy WB *et al*. Group treatment of premature ejaculation. *Arch Sex Behav* 1974; **3**: 443–452.
- Chatterjee R, Kottaridis PD, Lees WR *et al*. Cavernosal arterial insufficiency and erectile dysfunction in recipients of high-dose chemotherapy and total body irradiation for multiple myeloma. *Lancet* 2000; **355**: 1335–1336.
- Chatterjee R, Andrews HO, McGarrigle HH *et al*. Cavernosal arterial insufficiency is a major component of erectile dysfunction in some recipients of high-dose chemotherapy/chemoradiotherapy for haematological malignancies. *Bone Marrow Transplant* 2000; **25**: 1185–1189.
- NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993; **270**: 83–90.
- Howell S, Shalet S. Gonadal damage from chemotherapy and

- radiotherapy. *Endocrinol Metab Clin North Am* 1998; **27**: 927–943.
- 9 Chatterjee R, Mills W, Katz M *et al*. Germ cell failure and Leydig cell insufficiency in post-pubertal males after autologous bone marrow transplantation with BEAM for lymphoma. *Bone Marrow Transplant* 1994; **13**: 519–522.
 - 10 Howell SJ, Radford JA, Smets EM, Shalet SM. Fatigue, sexual function and mood following treatment for haematological malignancy: the impact of mild Leydig cell dysfunction. *Br J Cancer* 2000; **82**: 789–793.
 - 11 Maggi M, Filippi S, Ledda F *et al*. Erectile dysfunction: from biochemical pharmacology to advances in medical therapy. *Eur J Endocrinol* 2000; **143**: 143–154.
 - 12 Goldstein I, Lue TF, Padma-Nathan H *et al*. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *New Engl J Med* 1998; **338**: 1397–1404.
 - 13 Lue TF. Erectile dysfunction. *New Engl J Med* 2000; **342**: 1802–1813.
 - 14 Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000; **164**: 371–375.
 - 15 Levy A, Crowley T, Gingell C. Non-surgical management of erectile dysfunction. *Clin Endocrinol* 2000; **52**: 253–260.
 - 16 Aversa A, Isidori AM, De Martino MU *et al*. Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. *Clin Endocrinol* 2000; **53**: 517–522.
 - 17 Jannini EA, Screponi E, Carosa E *et al*. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *Int J Androl* 1999; **22**: 385–392.
 - 18 Hafez B. Recent advances in clinical/molecular andrology. *Arch Androl* 1998; **40**: 187–210.