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Brief Correspondence

Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study

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Abstract

Evidence from animal models replicating postradical prostatectomy erectile dysfunction (pRP-ED) suggests intracavernous injection of bone marrow-mononuclear cells (BM-MNCs) as a promising treatment approach for pRP-ED. We conducted a phase 1/2 pilot clinical trial of intracavernous autologous BM-MNC injection to treat pRP-ED (NCT01089387). Twelve patients with localized prostate cancer and vasculogenic pRP-ED refractory to maximal medical treatment were divided into four equal groups treated with escalating BM-MNC doses (2×10^7, 2×10^8, 1×10^9, 2×10^9). Tolerance was the primary endpoint. Secondary endpoints were the effects on erectile function and penile vascularization at 6 mo, as assessed using the International Index of Erectile Function-15 and Erection Hardness Scale questionnaires, and color duplex Doppler ultrasound. We measured the peak systolic velocity in cavernous arteries and assessed endothelial function using the penile nitric oxide release test.

No serious side effects occurred. At 6 mo versus baseline, significant improvements of intercourse satisfaction (6.8 ± 3.6, 3.9 ± 2.5, $p = 0.044$) and erectile function (17.4 ± 8.9, 7.3 ± 4.5, $p = 0.006$) domains of the International Index of Erectile Function-15 and Erection Hardness Scale (2.6 ± 1.1, 1.3 ± 0.8, $p = 0.008$) were observed in the total population. Spontaneous erections showed significantly greater improvement with the higher doses. Clinical benefits were associated with improvement of peak systolic velocity and of % penile nitric oxide release test and sustained after 1 yr. Our results need to be confirmed by phase 2 clinical trials.

Patient summary: We report a phase 1/2 pilot clinical trial investigating cell therapy with injection of bone marrow mononucleated cells to treat postradical prostatectomy erectile dysfunction. No serious side effects occurred. Improvements of erectile function and penile vascularization were noted. Further studies are required to confirm these preliminary results.

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1. Introduction

Radical prostatectomy (RP) remains the reference treatment for organ-confined prostate cancer. Despite technological improvements, RP still carries a risk of postoperative erectile dysfunction (ED) [1]. Postradical prostatectomy erectile dysfunction (pRP-ED) results from injury to the penile neurovascular bundles that course along the posterolateral aspects of the prostate. Prolonged neurapraxia may result in corporeal fibrosis and veno-occlusive dysfunction. These structural alterations are associated with penile shortening and irreversible ED [2]. Injury to an accessory pudendal artery may contribute to the vascular component of pRP-ED [3,4].

Recent pathophysiological insights provided by animal studies have led to the development of cell-based therapies for pRP-ED using intracavernous injections of stem cells obtained from adipose tissue [5,6] or bone marrow [7]. We previously showed in rats that intracavernous injections of bone marrow mononuclear cells (BM-MNCs) corrected the histological and functional abnormalities caused by cavernous nerves ablation [7]. BM-MNCs are a heterogeneous population of cells including mesenchymal stem cells, endothelial progenitor cells, and hematopoietic stem cells. BM-MNCs may exert antiapoptotic, neurotrophic, and angiogenic effects [6,7].

Here, we report the results of a 1-yr, nonrandomized, dose-escalation, phase 1/2 pilot clinical trial investigating intracavernous injection of BM-MNCs in patients with severe pRP-ED (NCT01089387). Inclusion criteria are described in the Supplementary data. Briefly, we included 12 men aged 45–70 yr who had had RP 6 mo to 3 yr earlier to treat a localized prostate adenocarcinoma. The other inclusion criteria were pRP-ED with penile arterial insufficiency and/or veno-occlusive dysfunction documented using color duplex Doppler ultrasound (CDDU), and failure of pharmacotherapy defined as an Erection Hardness Score (EHS) <3 after at least 10 intracavernous alprostadil injections (20 μg) combined with sildenafil (100 mg) and the use of a vacuum device. We considered that the association of vasculogenic pRP-ED and resistance to maximal medical treatment indicated end-organ failure and a very low likelihood of recovering sexual function with or without erectogenic pharmacotherapy [8–10], regardless of the status of penile neurovascular bundle preservation indicated in the operating report of RP.

The primary objective was to assess the safety of four doses of intracavernous BM-MNCs used to treat pRP-ED (2×10^7, 2×10^8, 1×10^9, and 2×10^9) in 12 consecutive patients within 6 mo after the injection. Each patient received one injection. The preparation process of BM-MNCs is described in the Supplementary data. The secondary objectives were to evaluate effects of BM-MNC injection on sexual function, penile vascularization, endothelial function, and change in penile length. Sexual function was evaluated at baseline then 1-mo, 3-mo, 6-mo, and 12-mo postinjection, using the EHS with and without the use of erectogenic drugs and the International Index of Erectile Function-15. Penile vascularization was evaluated with CDDU as described in the Supplementary data. We measured the peak systolic velocity in cavernous arteries (PSV) and assessed endothelial function using the penile nitric oxide release test. The assessment of cavernous nerve injury and the potential neurotrophic effects of BM-MNCs nerves cannot be evaluated in human patients with standard procedures. We therefore focused our attention on the vascular component of pRP-EP that can be monitored using CDDU. Statistical analyses are described in the Supplementary data.

The mean age of the 12 patients was 63.6 ± 4.2 yr and the mean time from RP to BM-MNC injection was 22.9 ± 9.8 mo. The characteristics of the patient population at baseline and the characterization of injected BM-MNCs are described in the Supplementary data.

Mild postoperative pain at the BM aspiration site (mean visual analogue scale score, 2 ± 1) was the most common side effect. No patient reported pain at the 1-mo visit. No cases of priapism were recorded. In the three patients of the third-highest dose group, late bacterial growth ($>$10-d postinjection) of the cutaneous saprophyte *Propionibacterium* was observed in the BM samples. No clinical effects were recorded; more specifically, no patients experienced local abscess or fever after BM-MNC injection. For the last three patients, we used a barrier drape (Steri-Drape, 3 M, USA) to cover the posterior iliac crests during BM aspiration, and no further bacterial contamination occurred. Mean hemoglobin decreased by -1.9 ± 0.7 g/dl overall on the postoperative day. The decreases were larger in the two highest dose groups (dose 3, -1.9 ± 0.3 g/dl; dose 4, -2.9 ± 0.4 g/dl) than in the two lowest dose groups (dose 1, -1.4 ± 0.4 g/dl; dose 2, -1.4 ± 0.3 g/dl). No patient required blood transfusion. At all follow-up visits, prostate-specific antigen was undetectable in all patients and digital rectal examination showed no evidence of local recurrence.

BM-MNC injection significantly improved most of the sexual scores at 6 mo (Table 1). At 6 mo versus baseline, mean gains were $+1.3 \pm 1$ for on-medication EHS, $+0.8 \pm 1.2$ for off-medication EHS, and $+10.1 \pm 8.6$ for The International Index of Erectile Function-15-erectile function subscore. Overall, nine out of 12 patients reported successful intercourses with vaginal penetration on medication. Comparing the four dose groups, they showed no significant differences in sexual scores (Supplementary Fig. 1). However, the off-medication EHS at 6 mo exhibited a greater improvement with the two highest doses ($+1.3 \pm 1.5$) compared with $+0.2 \pm 0.4$ with the two lowest doses ($p = 0.012$), indicating a better improvement of natural erections for dose 3 and dose 4. Sexual function scores at 12 mo were not significantly different from those at 6 mo (Supplementary Fig. 2), suggesting sustained beneficial effects of BM-MNCs. Penile length was significantly increased versus baseline at 1 mo and 3 mo but not at 6 mo (Table 1). Basal and 20-min PSV increased significantly after BM-MNC injection (Table 2). At 6 mo, 20-min PSV was normal in seven of the 11 patients with baseline arterial insufficiency. When we used penile nitric oxide release test $>$35% as the cutoff to separate normal from abnormal, we found a significant increase in the proportion of patients with normal endothelial function at 6 mo compared with baseline (8/11 vs 2/11, $p = 0.032$).